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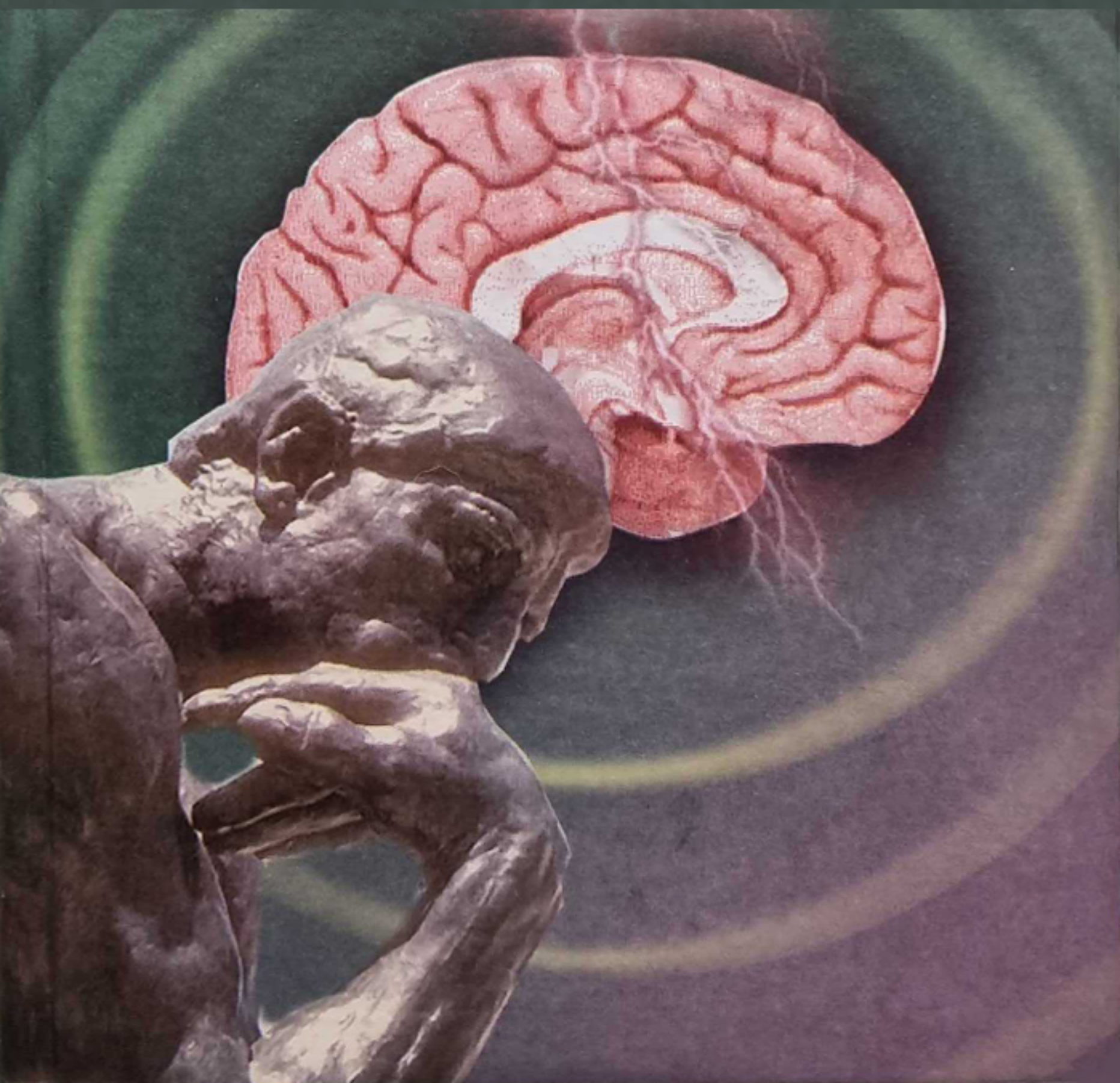
MEDICAL IMPROVEMENT
OF THE COGNITIVE BRAIN FUNCTION
(NOOTROPICS)



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MEDICAL IMPROVEMENT OF THE COGNITIVE BRAIN FUNCTION

(question-answer form)

Student Text Manual

Stavropol, 2016

Acknowledgments

"*The great events of the world take place in the brain*"
Oscar Wilde

This book has been translated through the initiative and dedication of Lev Fomchenkov, the Founder of CosmicNootropic.com, and with the invaluable support of passionate nootropic enthusiasts who contributed financially and shared information about the crowdfunding campaign within the nootropics community.

Your efforts made it possible to disseminate knowledge about nootropics and ensure that this book is accessible for everyone to read.

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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

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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.

CHAPTER III. MECHANISMS OF NOOTROPIC EFFECT

21. Question: How to reveal the nootropic action of medications experimentally and clinically?

Answer: The search for new drugs with nootropic properties is of course impossible without evaluating their action by means of adequate experimental simulation models at the preclinical stage of study, as well as in studies on healthy persons and those with health issues. Many experimental and clinical methods are valid for this purpose.

Experiments on animals allow us to evaluate almost all aspects of the pharmacology of potential and already used nootropics. Some methodological approaches are based on recording normal physiological parameters, while others rest on pathologically changed ones. These approaches make it possible to take into consideration the influence of medications on the main parameters of cognitive activity (memory, learning, perception, attention) as well as on electrophysiological and neurochemical processes which are associated with them (Voronina T.A., 1989; Voronina T.A., Ostrovskaya R.U., 2010).

A common psychophysiological method for studying behavior is a simulation of conditioned reflex of passive avoidance, which can be used to determine the pharmacological sensitivity of the memory and learning mechanisms in the first approximation. There are several modifications of this method, but the general idea is to form in an animal an urge to abstain passively from making any action. This avoidance reflex is usually simulated in a box with two sections, illuminated and darkened ones. A rat or a mouse, being placed in the first, illuminated part of the box, tries to get to the safer and darker part; but after it gets an electric shock there, preferring to avoid punishment it usually stays in place already in the second test. An injection of the studied substance before the training procedure makes it possible to determine the effect of this substance on the formation of the memory trace, and after training - on its consolidation.

Compared to the passive avoidance reflex, the active avoidance response is more challenging, when the animal has to perform a certain action to prevent punishment. The acquisition of the active avoidance response requires repeated exposure to both conditioned and unconditioned stimuli. In the course of repeated trials, animals make fewer and fewer mistakes, which allows us to follow up the learning process in a certain way. For this purpose a shuttle box is used most frequently; there a rat is supposed to leave the occupied compartment upon a conditioned signal (light or sound) in order to escape from the painful punishment.

Despite the popularity of both of these methods in experimental psychopharmacology, it is necessary to take into account the underlying negative emotional factor. Therefore, consolidation and accelerated development of a conditioned reflex during the administration of pharmacological substances may also depend on the presence of anti-anxiety properties in

their spectrum of action. Hence, not only nootropics, but also anxiolytics and antidepressants show effectiveness in such models. Undoubtedly psychomotor stimulants (caffeine, phenamine) also contribute to optimization of learning by facilitating motivation and motor acts.

Different types of maze models are also used to reveal the nootropic activity. Studying the behavior of rodents in a maze is considered to be a more adequate methodological approach, because their developed spatial memory allows them to learn and navigate more easily in such conditions. For example, different modifications of the radial maze consisting of several (4-16) arms are used; and only in some of them a hungry animal receives food reinforcement. This task corresponds in many ways to the search of food in the natural environment and makes it possible to assess the validity of the behavioral strategy. The nootropic effect is manifested in the reduction of the number of error runs and acceleration of learning. However, food motivation is important for skill shaping in this case; thus a stimulating or a depressing effect of substances on the appetite can noticeably distort the results.

Research conducted in the Morris water maze is devoid of this drawback. Here the animal is trained to search for a rescue platform as quickly as possible, and the avoidance of the experimental situation serves in itself as a positive reinforcement. With multiple repetitions of the experiment, some animals show that they acquire the spatial skill by decreasing the time to find an exit from the maze and by reducing the number of error swims into dead-end sections. Since the maze behavior reveals dependence on the functional state of cholinergic mechanisms which are closely related to memory organization, this model is considered to be the most suitable for the study of nootropic activity.

In addition to the assessment of behavior, electrophysiological methods are also used to describe the effects of substances. Additional criteria for an optimizing pharmacological effect on the brain are EEG shifts, reorganization of the spectral characteristics of electrical activity, changes in the latency and amplitude of sensory (visual, auditory, tactile) evoked potentials in the neocortex. For this purpose, researchers use stimulation of the peripheral receptor apparatus as well as subcortical parts of one or another analyzer with specific stimuli.

The registration of transcallosal evoked potentials is also considered an essential approach to assessing the pharmacology of nootropic drugs. This method can determine the efficiency of interhemispheric transfer of information with the involvement of the corpus callosum, whose dysfunction is responsible for memory and learning impairment. The study of transcallosal potentials is usually conducted on rabbits and cats; and individual parameters of the cortical response to stimulation of the symmetrical point of the opposite hemisphere are considered.

Along with that, it is quite obvious that the results of any studies conducted on healthy animals cannot be regarded as sufficiently correct when it comes to a specific nootropic effect. The necessary prerequisite for its identification is the existence of a cerebral pathology in the form of organic mental insufficiency. Therefore, data obtained through the methods described above, has to be supported by experiments on adequate models of cognitive

pathology with an impairment of primarily mnestic processes.

In order to simulate cognitive disorders, a variety of techniques are used. These include different ways of provoking amnesia as well as a simulation of brain diseases. For this purpose toxic or mechanical brain damage as well as different types of ischemic conditions and tissue hypoxia are used. We can talk with a certain confidence about a substance's nootropic activity only when it will not only be demonstrated on such models, but also differentiated in comparison with the effect of other psychotropic drugs.

The phenomenon of amnesia is quite often used as a model of cognitive pathology. Memory disturbances are induced using different methods, and the simplest ones in terms of methodology are injections of certain amnesic agents. Severe amnesia occurs after the administration of M-cholinoblockers (scopolamine, atropine), protein synthesis inhibitors (puromycin, actinomycin) or catecholamines (alpha-methyltyrosine). Memory can also be disturbed after convulsive seizures which are provoked with convulsants (picrotoxin, corazol) or a maximum electroconvulsive shock. Disturbance of not only mnestic, but also other cognitive functions is also simulated by means of strong stress exposure of animals. Deprivation of the paradoxical phase of sleep leads to the similar result.

To work with a pathology resembling that of aged people, atherosclerotic vascular lesions are simulated artificially by keeping rats and mice on a diet with high cholesterol levels. Studies are also conducted on old animals (14-19 month-old mice and 22-28 month-old rats). In such cases, the studied substances shall be administered chronically over a long period of time.

Behavioral and biochemical changes which occur in some types of neurointoxication, cerebral ischemia and hypoxia, are also similar to natural pathological conditions. A toxic agent capable of causing extensive and indiscriminate neurodegeneration is ethanol. It is even believed that the consequences of chronic alcoholism can serve as some kind of an analogue of Alzheimer's disease. More specific cognitive disorders develop after intracerebral injections of aziridine, a selective cholinergic neurotoxin, and toxic beta-amyloid peptide (Abeta compound) specific for Alzheimer-type lesions, or a damage of dopaminergic neurons by MPTP toxin which is used to simulate parkinsonism. The resulting behavioral and patho-morphological shifts are thought to be very similar to a neurodegenerative pathology in humans.

Since ischemic disturbances are the root cause of many diseases with cognitive disorders (stroke, traumatic brain injury), it is important to evaluate the effectiveness of substances with potential nootropic activity in different models of cerebral ischemia. Global transient ischemia is reproduced by temporary ligation of both carotid arteries, and focal ischemia is usually simulated by the occlusion of the middle cerebral artery. Photoinduced thrombosis is proposed as a more adequate and noninvasive version of the latter. This method is based on injecting an animal with a photosensitive dye, followed by the local light exposure of a certain brain area, which produces a limited vascular defect close to an ischemic stroke.

Since various forms of organic mental insufficiency are accompanied to a greater or lesser extent by the tissue hypoxia, it is also necessary to study nootropic activity in different

models of hypoxia. It is simulated by the gradual replacement of oxygen with nitrogen in enclosed space or by the sodium nitrate injection in the form of hypobaric hypoxia in barochamber (hemic hypoxia). Sometimes it is necessary to assess the effect of nootropic agents in perinatal oxygen deficiency, for which pregnant animals are subjected to hypobaric hypoxia. However, it shall be taken into account that antihypoxic properties are typical of pharmacological drugs that not only improve but also worsen mnestic processes (for example, benzodiazepine anxiolytics); moreover, not all nootropics have antihypoxic effect.

In addition to experimental approaches, there are many techniques that can help determine the state of cognitive functions in clinically healthy and sick people. All research methods can be conditionally subdivided into card and hardware ones. The former are presented as a variety of questionnaires and scales, describing various aspects of personality and psychophysical status of the test person. The results give the right to assess the state of the short-term and long-term memory, active attention, and to evaluate the course of the thinking processes. By means of psychometric scales it is possible to quantitatively process the obtained material.

Among the most widespread psychophysiological methods, it is necessary to mention the Bourdon test and the Kraepelin test, which characterize a degree of fatigability and instability of attention, the battery of tests of the active memory aimed at estimating perception and memorization of visual and verbal information, the adaptive pathfinding test which takes into account visual-motor coordination, and a number of other ones. Often such approaches are combined with inventories that make it possible to describe the subject's personality from different angles, for example the Eysenck (in terms of extra-introversion) and the Spielberger-Hanin (different types of anxiety) inventories, the SAN test [*ed. note: Russian abbreviation - health, activity, mood*], the Minnesota Personality Test (MMPI), etc.

Hardware methods which are also presented in all possible variants, are united by the necessity of hardware launch (console) and registration of automated programs in case of presentation of visual and auditory signals with the subsequent computer processing of the data. Even though the card methods are inferior to the hardware ones in certain criteria, they are more frequently preferred due to their greater simplicity and, at the same time, sufficient validity. In psychopharmacology, both techniques are used to determine the effects of substances on cognitive functions, psychophysiological structure of behavior, and emotional reactivity.

The described techniques which are suitable for testing healthy people, are not always suitable and sometimes are not applicable at all in studies of patients with organic mental retardation. A more targeted choice of adequate approaches is needed depending on the person’s age and the type of pathology. In clinics, it is suggested to use a simplified scale to assess mental disorders, special tests (for example, Bumke) to determine geriatric memory, dementia scale, etc.

As the present data show, modern psychopharmacology has a sufficiently rich set of experimental and clinical techniques which at different stages of research allow to draw a fairly full picture of the pharmacodynamics of nootropic agents and, above all, to assess the origin of their specific activity.

22. Question: How do the neurochemical mechanisms of the hippocampus impact the nootropic effect?

Answer: Assuming that the hippocampus has functional properties important for cognitive activity, the drug intervention in its work must a priori already be a part of the mechanism of the specific action of nootropic agents. The validity of such a conclusion also follows from the fact that there is a wide presence of those neurotransmitter and neuromodulator mechanisms in this limbic formation, which are involved in the genesis of the cognitive pathology and the nootropic effect. It is easy to find a confirmation thereof in most of the answers that we offer regarding the review of the origin of the specific properties of nootropics.

Therefore, without repeating ourselves, we can refer to several other quite obvious arguments in favor of the above statement. And many experimental findings are made in the study of the most common nootropics of the pyrrolidone group. For instance, when recording evoked responses of the single hippocampal neurons in vivo and in vitro in brain slices, it was shown that the systemic administration and local application of piracetam and related compounds significantly enhanced the activity of pyramidal cells in the CA1 and CA3 fields. The efficiency of the LP (long-term potentiation) induced by tetanization of neurons of the granular layer, increased markedly as well. However, the underlying neurotransmitter processes can apparently be of different nature.

The key role in the stimulating effect of nefiracetam is likely played by an enhancement of the cholinergic synaptic function, since the effect was attenuated by the H-cholinoblocker mecamylamine, and not by selective NMDA-receptor antagonists. At the same time, aniracetam was found to have a clear activating effect on glutamatergic transmission, without significant change in cholinergic processes in hippocampal slices. Along with that, the nature of the effect of aniracetam depended on the substance concentration that was used: in low, nanomolar concentration, the activation of NMDA-receptors was observed, and in high concentration - the AMPA-receptor activation.

The described results were obtained in brain studies of normal animals without any signs of cerebral pathology, although it is known that only its presence allows us to speak about the specifics of the observed shifts. Therefore, it is of particular interest to study the data on the use of nootropic agents in experimental models with cognitive dysfunction caused by hippocampal dysfunction. Thus, the implantation of Abeta compound (a fragment of beta-amyloid peptide, which is of particular importance in the genesis of Alzheimer's disease) into the rat hippocampus and/or the occlusion of the common carotid artery, simultaneously with amnesia, drastically activated local neuronal death on the principle of apoptosis. Preventive administration of citicoline which has cholinergic properties and enhances phospholipid biosynthesis, significantly limited cell death. This correlated with the facilitation of passive avoidance learning as an indicator of the anti-amnestic effect.

Similar data are presented for the epiphyseal hormone melatonin which, in our opinion, can qualify for the position of an endogenous nootropic compound. Old rats after a bilateral

intrahippocampal injection of the beta-amyloid protein showed massive damage to cellular elements, which coincided with the deterioration of spatial orientation in the water maze. The use of the hormone could halt the destructive phenomena in the brain tissue with a parallel improvement of memory and learning in the form of a more successful solution of the behavioral task. Melatonin also had a protective effect on the hippocampal neurons of the CA1 field in animals in case of transient brain ischemia.

The use of the epiphyseal hormone which is a chronotropic agent, made it possible to identify another curious fact. Its introduction into the incubation medium where the hippocampal slices of old mice were located, increased the amplitude of the evoked electrical response, the intensity of which was markedly impacted by the photoperiodic mode of pre-habitation of animals. The presence of additional dysrhythmia, a chronobiological defect, increased the hippocampal response to the substance.

The nerve growth factors are also capable of successfully protecting the hippocampal neurons from damage. If the synthesis of one of them (BDNF) in the dentate gyrus of the structure was locally disrupted, there was a sharp deterioration of the animals' memory. But when the production of this neurotrophin in the granular cells of the CA3 field was activated with a new anti-amnestic compound riluzole there was a marked improvement in memory.

These facts and those cited in other answers leave no room for doubt about the direct interest of the neurochemical mechanisms of the hippocampus with its mnestic, emotiogenic, and chronotropic properties in the origin of the nootropic activity of the medications.

23. Question: How do nootropics influence vision?

Answer: Almost any nootropic drugs regardless of their origin and mechanism of cellular action are supposed to improve vision a priori. This effect most likely serves as part of their specific action if we recognize the visual disturbance as an obligatory, pathogenetically significant factor in cognitive disorders. This statement can be illustrated by studying the pharmacodynamics of nootropics from various pharmacological groups.

First of all, an optimizing effect on the function of the visual analyzer is convincingly shown in some representatives of the pyrrolidone group. An intravenous injection of high doses of piracetam to patients with severe cognitive impairment who suffer from discirculatory encephalopathy or who had a traumatic brain injury, weakened amnesia and simultaneously improved visual-spatial perception, and according to ophthalmoscopy data, it increased the pulse blood filling of retinal vessels and increased venous outflow.

In evidence that the effect of piracetam can be achieved already at the level of the retina, it is reasonable to consider the results of our campimetric study of the visual function in persons who have suffered a traumatic brain injury in the past. Chronic oral administration of the substance, even at a relatively low dose, significantly reduced thresholds of retinal responses to light and color stimuli compared with placebo administration. More pronounced shifts were noted in subjects with a history of more severe traumatic brain injury. Piracetam also shortened the time of visual-motor reactions and increased the accuracy of visual task solving by patients with parkinsonism.

An optimizing effect on vision is also shown in picamilon, a combination drug of GABA and nicotinic acid. It is important to note that it proved to be effective in the treatment of primary ophthalmic pathology. Picamilon improved visual function and psychophysiological status in patients with central chorioretinal dystrophies, with pigmentary abiotrophy. Under its influence there was an expansion of the visual field and improvement of dark adaptation, which coincided with the normalization of the blood flow in the retina and reduction of vascular permeability.

Experimental analysis of the effects of piracetam and GABA-mimetic nootropics indicated that an improvement of sensory processes can depend not only on the direct normalization of the retinal hemodynamics and metabolism, but also on the intervention in the work of the central parts of the visual analyzer. Thus, when rabbits were trained to distinguish visual signals, piracetam facilitated differentiation of inhibitory and reinforced light flashes by single cortical neurons. Application of GABA and muscimol directly to the surface of the visual cortex of old monkeys increased the effectiveness of cortical cell responses to visual stimuli, and facilitation of interhemispheric transfer of visual information through the corpus collosum was found in rats. In this context, it is necessary to note that aniracetam has been shown to enhance the response to light flashes in single neurons of the hypothalamic suprachiasmatic nuclei with their rhythm-organizing properties in relation to circadian periodism.

Stimulation of the central and peripheral cholinergic transmission, inherent in various nootropic agents, is also associated with the optimization of the visual function. Administration of choline, a precursor of acetylcholine, in the form of citicoline to people with the functional blindness weakened its manifestations, which correlated with an increase in the amplitude of the evoked visual potentials in the neocortex. In part, this could be due to a direct effect of the substance on retinal neurochemical mechanisms since in rats it significantly increased the dopamine content in the retina.

Another stimulator of cholinergic synapses, acetyl-L-carnitine, shortened the latent period and increased the late (P300) wave of the evoked visual potential in monkeys, simultaneously facilitating the visual decoding task. When parkinsonism was simulated in primates with MPTP neurotoxin, a decrease in the severity of neurological symptoms under the influence of acetyl-L-carnitine was accompanied by an improvement in the electroretinographic indicators. One of the reasons for the normalization of the visual function by cholinergic agents can be the enhancement of H-cholinergic transmission. At least in experiments on rats it was found that nicotine was able to dose-dependently facilitate the development of a conditioned skill related to the visual task, and mecamylamine, a specific blocker of H-cholinoreceptors, had the opposite effect.

A large group of nootropics is represented by hormonal preparations (questions 39 and 40). Semax (a derivative of ACTH4-10) when administered intranasally to healthy individuals reduced the number of errors in operative memory tests, decreased response thresholds to color stimuli and increased the critical frequency of flicker fusion, and in people with consequences of traumatic brain injury it expanded the visual field and increased retinal color sensitivity. The effect of semax on vision may be determined not only by its central

properties but also by peripheral ones. As shown in patients with optic nerve lesions, the substance, expanding the total field of vision and increasing its acuity, enhanced the electric sensitivity and conductivity of the optic nerve with a limitation of atrophic processes in it.

A hypothalamic preparation of thyrolyberine also improved the functional state of the retina and normalized retinal metabolism, being particularly successful against the background of previous dystrophic changes. Hormonal compounds of the sex glands also optimize vision. If ovariectomized monkeys showed defects in the visual-spatial orientation and attention without changes in the speed of visual task solving, a prolonged administration of estradiol eliminated such disorders. Since estrogen also eliminates scopolamine-induced impairment of visual attention, it is believed that its action is due to an improvement of cholinergic mechanisms.

Given the active role of melatonin in retinal processes, it is not surprising that this natural nootropic can also have a favorable effect on vision. Chronic use of the hormone by the elderly who were found to have age-related decreased reactivity of the retina, contributed to an increase in its light and color sensitivity. According to campimetric data, the effect of melatonin is particularly pronounced in the peripheral areas of the retina.

In addition to these facts we can say that other drugs with nootropic activity also contribute to an improvement of the visual function. Thus in patients with partial optic nerve atrophy, cerebrolysin markedly improved visual acuity apparently due to an activation of the retinal metabolism and hemodynamics. Certain benzodiazepine anxiolytics as well as centrally stimulating agents (caffeine, eleutherococcus) also induce optimization of the visual perception, apparently, due to their primary influence on the emotional sphere.

The data set forth herein allows us to conclude that an improvement of the visual analyzer function is a universal property which is inherent in a variety of nootropic compounds. It can be based on different mechanisms related to the fact that the drugs can selectively, and more often simultaneously, modulate the work of both peripheral (retinal) and central parts of the visual system. Taking into account the important contribution of vision to the cognitive activity of the brain, the described property of nootropics shall be recognized as an indispensable element of their therapeutic activity.

24. Question: Do nootropics have a chronotropic action? And if they do, is it connected with a specific action of the substances?

Answer: The rhythmic nature of cognitive activity and the dependence of its disorders on circadian dysrhythmia allow for either possibility. We can refer to a number of experimental and clinical evidences of non-stationarity of the nootropic effect and its connection with the attenuation of biorhythm disorganization. This prompts us to consider in earnest the prospects of the therapy of cognitive disorders from a new, chronobiological perspective.

First of all, drugs of this class change the rhythm of normal and pre-disorganized behavior and contribute to the correction of mnestic disturbances caused by unfavorable, rhythm-destabilizing influences. The similar point is quite obviously illustrated by the study

of the sleep-wake cycle. Second of all, their effect is nonstationary in time and it distinctly fluctuates throughout the day just like the effect of other psychotropic drugs.

As a rule, therapeutic capabilities of nootropic agents in sleep disorders are rarely discussed since insomnia is included in the standard set of adverse reactions of the nootropic therapy. Meanwhile, they are capable of eliminating disorganization of circadian periodism, especially that of hypoxic origin, although to a different degree.

Thus, reduced oxygen content in the inhaled air provoked disturbances in the EEG pattern of sleep with a shortened REM phase in rats, and such dysrhythmia was eliminated already after a single use of small doses (30 or 100 mg/kg) of piracetam. Such experimental findings coincide with the results of studies of mexidol, for example, which has distinct antihypoxic properties. It successfully eliminated insomnia in almost one third of patients with cerebral ischemia, suppressing post- and intrasomniac phenomena. When treated with anticholinesterase compounds (tacrine, donepezil), patients who suffered from dementia and Alzheimer's disease also demonstrated normalization of night sleep simultaneously with improved cognitive indicators. The endogenous nootropic epiphyseal hormone melatonin has well-defined hypnogenic activity. It shall also be borne in mind that the combination of certain nootropic agents (for example, aniracetam) with traditional sleeping pills can significantly increase the effectiveness of the latter. In other words, under certain circumstances, nootropics of various types reveal the ability to limit circadian dysrhythmia and restore the basal sleep-wake cycle.

Similar rhythm-organizing activity has been shown in them in other chronobiological models. These include, in particular, paradoxical sleep deprivation which is accompanied by various EEG and behavioral disturbances such as pronounced amnesia and, at the cellular level, a destruction of mitochondrial membranes, accumulation of lipid peroxidation products, and a decrease in brain phospholipid content. Dysrhythmia, induced by sleep deprivation, and biochemical shifts were weakened against the background of prior administration of piracetam or mexidol, and nicergoline even surpassed them in the strength of its anti-amnesic effect.

It is known that cognitive processes are closely connected with emotional reactivity. Anxiety and repeated stressing often aggravate mnestic activity, and along with that they cause destabilization of biorhythms of different periods. Anxiolytic drugs are shown to have synchronizing, rhythm-stabilizing activity, which correlates with the intensity of their anti-anxiety action. As we have found in the example of melatonin with its simultaneously anxiolytic, chronotropic, and nootropic properties, all three effects appear to be inherent in substances capable of normalizing the cognitive function.

Consequently, there is enough ground to suggest the specific activity of nootropic agents as a chronopharmacological phenomenon. Its origin shall be a priori determined by the pharmacological modulation of the work of the central apparatuses that control biorhythms. Indeed, substances can actively interfere with the function of secondary oscillatory brain formations such as the hippocampus and striatum, as well as individual elements of the chronobiological axis that has the leading role in circadian periodism: retina-suprachiasmatic nuclei of the hypothalamus-epiphysis.

The probability of a direct effect of nootropics on the activity of the main pacemaker mechanism is convincingly evidenced by the results of the study by Moriya et al (2003) obtained on slices of rat suprachiasmatic nuclei. Local application of aniracetam to neurons enhanced the ability of AMPA to increase the intracellular content of calcium ions and their responses to optic chiasma stimulation, and increased the induction of c-Fos protein with light. In vivo repeated administration of aniracetam potentiated the delay of the phase of the behavioral rhythm induced by short light slip during an early dark period, and this shift was prevented by the NMDA-receptor blocker dizocilpine.

The functional state of the suprachiasmatic nuclei and organization of circadian periodism in general largely depend on external illumination, the light time sensor, and therefore on the work of the visual apparatus, whose importance for mnestic processes was reviewed separately. Here it is relevant to remind that the retina by virtue of the features of its neurochemical organization can serve as the primary target for psychopharmacological influence, and that the epiphyseal melatonin which is a natural chronobiotic and nootropic, is capable to increase its light sensitivity in elderly people.

Along with that, individuals who have suffered a traumatic brain injury retain impaired light and color perception even in the long term after an event as compared to healthy individuals. On this background, piracetam clearly had an optimizing effect, lowering the threshold of brightness sensitivity of the retina. In this way, the substance can have a certain secondary effect on the formation of a clearer diurnal rhythm.

A special place in the genesis of behavioral dysrhythmias, as already indicated, belongs to a functional failure of the epiphysis and a disruption of melatonin production. There is enough evidence to confidently consider it as a natural nootropic agent capable of improving cognitive processes through a variety of mechanisms. Analyzing this problem, we have deliberately neglected, perhaps, the main pharmacological effect of the hormone, related to its stabilizing influence on the disorganized rhythmics. Meanwhile, it is this property of melatonin that has gained application in modern clinical practice. Therefore, it is reasonable to examine the nootropic capabilities of the hormone primarily from chronobiological standpoints.

There is an extensive literature and experience of our own studies that allow characterizing the chronotropic activity of melatonin in different aspects. First of all, it manifests itself in distinct synchronization of circadian rhythms of locomotor activity, hormone secretion, and the function of internal organs in experimental animals in case of repeated administration of melatonin. In contrast, after the removal of epiphysis, phase desynchronization of oscillations and difficulty in their resynchronization take place.

Obviously, the normalizing effect of melatonin on sleep shall be considered as a part of its synchronizing properties. A significant number of papers are devoted to this issue, due to this the hormone has firmly mastered its reputation as a good hypnotic. According to studies in humans, exogenous melatonin, in addition to reduction of the feeling of tension and anxiety, also facilitates falling asleep and restores the phase structure of sleep; along with this its hypnogenic activity often correlates with the curve of the daily hormone secretion and body temperature.

It has been convincingly proven that it is particularly effective in the elderly suffering from insomnia, and curiously enough, even when used at extremely low doses (0.1-0.3 mg). In the case of long-term use of melatonin, sleep also improved in patients with Alzheimer's disease. It is important to note that gradual development of reliable sleep in those patients went in parallel with the weakening of cognitive disorders.

Another common reason for using the chronotropic properties of the hormone is preventive and therapeutic prescription in the fight against latitudinal desynchronosis, primarily in airliner crews and passengers. Even when applied in small doses before and after transmeridian flights it promotes fast resynchronization of the rhythms, restoration of mental and physical efficiency, and mood elevation. The same applies to its effect on desynchronosis in workers of certain professions (nurses, policemen, etc.) engaged in shift work.

Taking into consideration the given data, the rhythm-organizing and hypnogenic activity of melatonin, in combination with other properties, shall be an important and obligatory component of the therapeutic possibilities of the hormone in the treatment of cognitive disorders. However, the most distinct effect can be rightly expected in cases when they are provoked by primary dysrhythmia. Still, in a recent symposium on therapeutic potential of melatonin it was noted that although sleep disturbances and circadian periodism are common indicators for prescribing the substance, it has a much richer set of clinically valuable properties. And the nootropic one, as we could witness, belongs to them.

The significance and prospects of the chronobiological approach in the treatment of cognitive pathology is also emphasized by an existence of non-drug rhythmogenic methods of combating it. Such methods include, for example, phototherapy, aimed at organizing a clear diurnal periodism. With its help it is even possible to weaken extrapyramidal symptoms and cognitive defects in patients with Parkinson's. Taking into account the pathogenetic similarity of this disease and a psychic depression, including the presence of signs of internal desynchronosis, deprivation of the REM phase of night sleep turns out quite effective in both cases. Several sessions of staying in a low-frequency electromagnetic field also lead to an improvement of memory and visual perception in patients with neurodegenerative brain diseases (Alzheimer's and Parkinson's diseases).

25. Question: Do nootropics ensure an anti-ischemic effect, and to what extent does their specific action correlate with brain vasodilation?

Answer: The first part of the question can be answered affirmatively with no further comment because the main point of the nootropic effect, one way or another, comes down to mitigation of the symptoms of cerebral ischemia and its consequences. As for the existence of vasodilator properties in nootropics, this question shall be considered in two aspects: do drugs with primary vasodilator activity also weaken cognitive impairment; and is vasodilator activity a mandatory component of the specific action of nootropic drugs?

The first aspect of the problem is probably the most difficult one, because primary vasodilation is not always possible and is not even required at all times.

Modern medicine has an extremely rich arsenal of vasodilators, used mainly in the

treatment of arterial hypertension. However, their use in combating cerebrovascular pathology is extremely rare. As it happens, most antihypertensive drugs are void of the ability to directly dilate cerebral vessels. And if we talk about systemic hypotension, it is justified only in those cases when the cause of an acute impairment of cerebral circulation is the hypertensive crisis. In other situations, a decrease of arterial pressure below a certain indicator is fraught with danger of a drop in the cerebral perfusion pressure, and therefore aggravation of ischemia.

Only a relatively narrow range of drugs can have a direct vasodilatory effect, thereby normalizing cerebral hemodynamics and improving mental activity. These include GABA and its preparations (aminalon, picamilon), purine derivatives (pentoxifylline) and nicotinic acid (xanthinol nicotinate), ergot alkaloids (nicergoline) and periwinkle (vinpocetine), as well as calcium channel blockers (nimodipine, cinnarizine). All of them in different ways relax vascular smooth muscle and restore blood circulation in the ischemic brain with optimization of cognitive processes.

However, a number of obstacles hinder the manifestation of the therapeutic potential and a wide use of vasodilating nootropics in practice. In particular, it is not always possible to use vasodilation as the main therapeutic approach. Such substances are of little or no effectiveness in patients with severe atherosclerotic lesions of cerebral vessels that have lost their ability to dilate. In the presence of epy local ischemic foci, by causing the dilatation of the vascular bed in healthy parts of the brain such substances may provoke the 'steal phenomenon' because of the additional worsening of the blood flow in the affected area. It is risky to use genuine vasodilators in early stages of traumatic brain injury or hemorrhagic stroke, when the healthy tissue surrounding the hemorrhage does not need hyperemia and stimulation of metabolism, but, on the contrary, requires a reduction in the need of oxygen and nutrients, and the formation of hypothermic (anabiotic) state.

Lastly, it shall be borne in mind that for some nootropics that seem to be pure vasodilators, the mechanism of their cellular action is still largely unclear. And there is a chance that it is not the dilatation that determines the drug's therapeutic merits after all.

This provision is convincingly illustrated by an example of pentoxifylline, a xanthine derivative commonly regarded as a typical vasodilator. Meanwhile, as it turned out, it does not so much dilate the cerebral vessels as it optimizes the rheological properties of blood. This is manifested in a reduction of fibrinogen level, a reduction of erythrocyte aggregation and an improvement of their filtering property (deformability). The effect of pentoxifylline on leukocytes, which activation invariably accompanies occlusive arteriopathies, is found to be equally important. Under the influence of the substance, granulocyte and macrophage content changes with a limitation of the formation of anti-inflammatory cytokines; cellular interaction changes as well. All this together significantly improves the blood flow in the microcirculation system and increases the oxygenation of brain areas in the ischemic zone.

Another traditional vasodilator, vinpocetine, also stands out for its multicomponent mechanism of action. In particular, it was found to have pronounced neuroprotective properties. They manifest themselves in a stronger reduction of pathologically elevated levels of calcium ions in hippocampal pyramids and in more significant antioxidant activity,

compared with piracetam. Vinpocetine limits glutamate excitotoxicity by the blockade of AMPA receptors while promoting the accumulation of adenosine in the brain tissue through the inhibition of its reuptake. According to positron-emission tomography data, it improves glucose transport across the blood-brain barrier in patients with chronic ischemic stroke. In other words, similar to pentoxifylline, the forefront of the therapeutic effect of vinpocetine is not necessarily its vasodilator activity.

Thus, although certain nootropic agents are sometimes regarded as primary vasodilators, the origin and merits of a ‘pure’ dilatation in combating cerebral ischemia and cognitive pathology are by no means indisputable.

But the second part of the question posed at the beginning - whether there is a vasodilator component in the anti-ischemic action of nootropic agents - shall definitely have an affirmative answer. It has already been noted earlier that any increase in neuronal activity is necessarily accompanied by physiological hyperemia of that part of the brain which is directly related to a certain type of activity. Hence, in our opinion, it is already obvious a priori that any form of drug stimulation of the work of nerve cells shall also be accompanied by an increase in the cerebral blood flow of secondary origin. The results of a considerable number of modern studies support the validity of such an a priori assumption.

For example, a lot of data has been presented in favor of the existence of vasodilatory properties in GABA and its derivatives. This provision is justified with an example of piracetam both in early studies using the method of hydrogen clearance and later in positron-emission tomography.

With all the credibility of this data, it must be noted that way back in the 1970s Herrschaft (1978) in the process of evaluation of the effect of piracetam on regional blood flow in patients with acute cerebral ischemia, paid attention to an occurrence of the hemodynamic response to it only in gray matter of the brain but not in the white one. The researcher assumed that the established fact could testify that there is an indirect, secondary nature of vasodilation induced by the primary effect of the substance on the neuronal activity. The existence of vasodilator properties in racetams that do not impact GABAergic transmission allows for this possibility, at least as part of the pharmacological response. The ability of these nootropics to improve blood rheological parameters in the form of weakening of erythrocyte aggregation, increasing their deformability and, ultimately, increasing blood fluidity does not allow attributing a therapeutic potential of piracetam and similar compounds entirely to vasodilation.

The study of substances with synaptotropic properties even more evidently demonstrates secondary, reactive hyperemia after an administration of nootropic drugs. The results of the study of very popular cholinomimetic agents prove this convincingly. Prescription of anticholinesterase compounds of donepezil and rivastigmine to persons suffering from Alzheimer's disease with cholinergic deficiency and cerebral circulatory insufficiency characteristic of the disease, attenuated both disorders. According to the single-photon emission computed tomography data, the blood flow increased most clearly in the frontal and temporal lobes of the brain, with a stronger increase in patients who responded to the therapy with improved psychophysiological indicators.

Similar results were obtained in experiments on rats and monkeys when assessing cerebrovascular circulation with the same informative method after an administration of physostigmine and tacrine. Both preparations dilated cerebral vessels, but they did it more successfully in old animals compared to young ones; and the effect was much more distinct in the hemisphere where the ascending cholinergic projections from the basal nucleus of Meinert were morphologically damaged. Clear vasodilator and neuroprotective shifts were also found after the use of acetylcholine precursor choline in citicoline composition. In animals with the basal artery occlusion or subarachnoid hemorrhage, the drug limited the scale of an ischemic lesion and even reduced the volume of small infarctions. Several days after reperfusion, edema and neuronal death in the CA1 field of the hippocampus were also attenuated.

The dilation of cerebral vessels also accompanies multidirectional interference in glutamatergic transmission. This effect is caused by its disruption by the NMDA-receptor antagonist dizocilpine. Mitigation of cerebral ischemia with nicergoline is also partially associated with a reduction of glutamate levels in the brain tissue due to an enhancement of its reuptake by presynaptic endings. On the other hand, an increase in the activity of glutamatergic synapses, probably under the conditions of initial hypofunction, also contributes to an increase in the cerebral blood flow. Thus, the elimination of ischemia and improvement of microcirculatory state in the neocortex are promoted by nooglutyl, which is a glutamic acid derivative recently created in the Russian Research Institute of Pharmacology. Significant anti-ischemic capabilities are also shown in a combination product which includes pyroglutamic acid and GABA-mimetic pyrrolidone.

Considering distinct vasodilatory properties of nootropics that interfere with various neurotransmitter processes, it is worth noting that the central dopamine mimetics have similar pharmacological activity. Judging by the results obtained in parkinsonism patients using the positron emission tomography method, the treatment with levodopa is accompanied by an enhancement of the cerebral circulation simultaneously with an improvement of psychomotor indices. A successful solution of mnestic tasks by patients is accompanied by an increase in the blood flow in the prefrontal neocortex.

The functional hyperemia that accompanies normalization of cognitive processes is also induced by hormonal drugs which demonstrate distinct nootropic properties irrespective of the hormone type. In global cerebral ischemia and experimental ischemic stroke in animals as well as in human patients in the acute period of ischemic stroke, the ACTH derivative Semax has proven to be effective. The hypothalamic hormone thyroliberin and its analogue talthyrylene prevented ischemic death of hippocampal neurons by optimizing cerebral hemodynamics. Likewise, the long-term substitution therapy with appropriate preparations of the sex hormones (testosterone and estradiol) in hypogonadal men and women markedly attenuated the extent of ischemic brain damage and defects in cognitive processes with increased perfusion of cerebral vessels.

Leaving such examples aside, we can conclude that the anti-ischemic effect is inherent in almost any nootropic agents, regardless of their type and mechanism of cellular action. The vasodilation that they induce is less often primary, but almost always has the character of a

secondary, functional hyperemia of cerebral structures. Subsequently, such hyperemia obviously becomes part of the specific activity of the substances.

26. Question: How does antihypoxic activity impact the nootropic effect?

Answer: Given the close connection of hypoxia with brain dysfunction and, in particular, with disturbances in cognitive processes and drastic consequences for neuronal activity, caused by it, the answer to the question seems obvious. Since ischemic hypoxia is a common companion of organic mental insufficiency of various origins, the fight against it must be a priori an indispensable element of the specific activity of nootropic agents. However, if we reframe the posed question like this: "Is elimination of hypoxia alone deemed sufficient enough to provide the nootropic effect?" - the answer would not be so straightforward.

Currently, drugs capable of 'pure' elimination of the functional manifestations of hypoxia are pharmacologically grouped under the name of antihypoxic drugs. A look at this group shows that with the exception of mexidol, it almost does not contain classic nootropics. Antihypoxic drugs themselves are proposed to be subdivided into substances of specific and nonspecific action. For the latter, elimination of hypoxia is a side effect in the profile of their pharmacological activity and it merely accompanies some main effect. Following this logic, it seems that it is this group that shall include agents for the treatment of cognitive pathology, whose antihypoxic effect is not considered to be determinant.

The validity of such a paradoxical, at first glance, conclusion is confirmed by the results of the correlation analysis of the conjugation of antihypoxic and purely nootropic, antiamnesic activity in a large number of antihypoxic drugs and nootropics. It turned out that in many cases there is no direct correlation between them. Moreover, there are drugs, such as peptide compounds, with a pronounced anti-amnesic effect that have no antihypoxic properties; and on the contrary, benzodiazepine anxiolytics that have antihypoxic effects, do not improve, but rather impair memory and learning. Dissociation of these effects is noted, for example, in the long-term use of certain nootropic agents. For example, in the case of months-long administration of nooglutil, a progressive improvement in memory is observed, although its antihypoxic activity is just as progressively decreasing.

While noting the absence of this correlation, at the same time we must admit that the antihypoxic component is nevertheless contained in the action of many nootropics and is not by any means of secondary importance for their clinical efficacy. Obviously, the therapeutic potential of drugs is largely determined by the extent (and, apparently, the ratio) to which their ability to withstand oxygen deficiency is combined with the nootropic activity itself. Substances with pronounced or moderate antihypoxic properties accompanied by anti-amnesic action (piracetam, nooglutil, mexidol) in the spectrum of their pharmacological activity are most successful in reducing cognitive disorders. Although compounds devoid of the antihypoxic component can also restore memory and learning, they are generally less effective.

In our opinion, in order to reconcile the seemingly obvious contradictions of the above

statements, it is necessary to take into account the nature of simulation states which are used to study the nootropic activity and, in particular, the presence or absence of the hypoxic factor. If this factor is present, we suggest using a classification approach that we propose below. If hypoxia acts as a pathogenetic link in mnestic disorders, it is legitimate to distinguish three types of nootropics:

1. substances that reduce the need of nerve cells for oxygen,
2. agents that enhance oxygen delivery to an ischemic part of the brain,
3. substances that eliminate the consequences of ischemic hypoxia.

Evidently, we are not talking about exclusive, but rather predominant intensity of manifestation of one or another property in certain compounds. There are still no drugs that would have all of the above properties in a 'pure' form. However, regardless of the peculiarities of the cellular action, the main point of the pharmacological fight against hypoxia will come down to elimination of the mismatch between the need of the brain tissue for oxygen and its supply, which shall directly correlate with the anti-amnesic effect.

Nootropic agents of the first group reduce the demand of cerebral tissue for oxygen in different ways. Since the leading cause of patho-chemical shifts caused by hypoxia is the disruption of the formation of high-energy compounds in cells, it is possible to increase their energy potential by enhancing oxidative or anaerobic carbohydrate transformations. This is supposed to lead to the secondary limitation of respiration. The ability to increase the energy capacity of neurons while weakening cognitive disorders has been shown in representatives of various groups of nootropics - pyrrolidone derivatives, acetyl-L-carnitine, extracts of Ginkgo biloba leaves, etc. In conditions of severe hypoxia, when it is impossible to restore the respiratory function of nerve cells, a similar result can be achieved by turning on the reserve ways of increasing energy, in particular, by means of activating glycolysis and better utilization of lactic acid.

Also, we shall not count out the possibility of a gradual increase of neuronal energy resources through gentle stimulation of their metabolism, when the increased consumption of macroergs is compensated by their stable resynthesis. Apparently, this is how psychotonic substances of plant origin work (ginseng, eleutherococcus, leuzea compounds, etc.).

Succinate oxidase pathway turned out to be a very promising reserve way to restore the energy potential of ischemic neurons, since the succinic acid as a substrate acts as an additional source of high-energy compounds. This pathway is actively used by GABA-mimetic nootropic agents. In cerebral hypoxia, the GABA shunt is triggered by oxidation of glutamate into GABA and then succinic half aldehyde into succinic acid. Similarly, succinate is incorporated into the tricarboxylic acid cycle and the respiratory chain, shunting the Krebs cycle. A typical agent with this type of action is sodium oxybutyrate (GHB). With its participation in mitochondria, the succinate-oxidase process of oxidation is triggered and simultaneously the deficit of the oxidized form of NAD is reduced. Due to this, GHB turns out to be effective in circulatory ischemia and seizures, although it shows weak nootropic properties.

But they are well expressed in mexidol, a complex preparation of succinate and 3-oxypyridine. In the composition of this preparation, the oxypyridine derivative which has

structural similarity to pyridoxine, is thought to facilitate the penetration of succinate into neurons and its subsequent oxidation, resulting in the primary normalization of energy metabolism. It is accompanied by restoration of pyridine nucleotides and flavoproteins in the mitochondrial respiratory chain. Yet, in addition to the described main effect, mexidol has a number of other therapeutically valuable properties that complement its nootropic activity and are associated with an effect on free radical processes (inhibition of LPO, activation of superoxide dismutase) and on the state of cell membranes (reduction of lipid layer viscosity, increase of fluidity).

Along with enhancement of cellular metabolism, increased resistance to oxygen deficiency can be achieved in the opposite way - by primary limitation of the intensity of cellular respiration. From this point of view, we can expect an antihypoxic, but not nootropic, effect from substances that inhibit neuronal activity. As a matter of fact, such an effect is characteristic of anesthetics, hypnotics, and anxiolytics, and it rather lines up with an impairment of memory and learning. Nevertheless, prescription of such drugs is justified in early ischemic hypoxia caused, for example, by a traumatic brain injury, in order to suspend further progression of the necrotic process.

The second group of nootropic agents with antihypoxic properties will consist of substances that improve the delivery of oxygen by blood to the focus of cerebral hypoxia by expanding cerebral vessels and improving cerebrovascular hemodynamics. These include nootropic vasodilators of different chemical structures.

By eliminating the insufficiency of cerebral circulation first, they secondarily eliminate circulatory hypoxia, which is an important component of their ability to improve cognitive activity. However, the therapeutic use of vasodilators faces certain problems. They are of little help and sometimes are even ineffective in elderly patients with severe atherosclerotic lesions of cerebral vessels, against the background of a sharp deterioration of vasomotor responses. In addition, vasodilators in case of regional ischemia, can induce the ‘steal’ phenomenon and aggravate hypoxia in the damaged area by further dilating the vessels of non-ischemic brain areas.

Finally, the third group of nootropic agents, which can be conventionally regarded as antihypoxic drugs, is represented by substances that eliminate negative effects of hypoxia. Such phenomena include, first of all, posthypoxic enhancement of free-radical processes, that inevitably go hand in hand with it. Therefore, all nootropics with antioxidant properties can be almost instantly considered as antihypoxic drugs. Indeed, in the pharmacology of antioxidant drugs, their therapeutic activity in essence is clearly associated with the primary antihypoxic properties.

Thus, the ability of medical compounds to eliminate manifestations of cerebral hypoxia, contrary to expectations, is not identical to the nootropic effect, although it plays a very significant role in the pharmacodynamics of nootropics. From the standpoint of this duality, depending on the mechanism of action, several groups of nootropic antioxidants can be distinguished. At the same time, it shall be emphasized once again that the reduction of hypoxia usually serves as only one component in the spectrum of pharmacological activity of the drugs.

27. Question: Does the nootropic activity depend on the antioxidant properties of medical substances?

Answer: Judging by the importance attributed to free-radical processes in neurodegeneration and the genesis of various types of organic mental retardation, combating them through antioxidant action shall a priori be an important element of the nootropic effect. Indeed, as recent studies show, this approach in pharmacology is very promising, and this has led to an emergence of the whole group of ‘pure’ antioxidants, some of which, however, are still at the preclinical stage of study. In the spectrum of pharmacological activity of the majority of modern nootropics, the antioxidant component, contrary to expectations, does not play a decisive role, although it is undoubtedly important.

Two approaches are valid for the limitation of the cytotoxicity of free radicals and the reduction of destructive effects of oxidative stress: primarily weaken free-radical processes, or eliminate the deficiency of the antioxidant system and achieve the identical result but in a secondary manner. Today, substances of different chemical structures are available separately or in a stack to solve one or the other task; according to preliminary data, they are quite suitable for the therapy and prevention of organic pathology of the brain.

Depending on the mechanism of cellular action and structure, it is recommended to distinguish several groups of antioxidants. They include substances acting as 'traps' of free radicals, blockers of the nitric oxide synthase, organic selenium compounds and 3-oxypyridine derivatives. Meanwhile, having a certain key property, representatives of each of these groups often exhibit a fairly wide range of antioxidant and non-antioxidant action.

Compounds from the nitrone group (phenyl-t-butyl-nitrone derivatives) and, in particular, one of them - PBN - have recently attracted great interest as ‘traps’ of free radicals. The ability to ‘trap’ hydroxyl, superoxide, and alkoxyl radicals is recognized to be the main source of the neuroprotective action of substances of this series. Meanwhile, under the influence of PBN, normalization of mitochondrial dysfunction, inhibition of glutamate neurotoxicity and anti-inflammatory cytokine activity, enhancement of cholinergic transmission due to inhibition of acetylcholinesterase, and restriction of apoptosis due to caspase inhibition are shown. It improves biochemical parameters, cognitive functions and limits neurological symptomatology in old animals as well as in various models of ischemic conditions. Its versatile mechanism of cellular action combined with a large therapeutic margin allows to consider PBN and some other nitrones with radical ‘trap’ properties as therapeutic drugs which can be very promising in the future.

The above said also applies in full to an organoselenium compound ebselen. This substance shows glutathione peroxidase activity and successfully blocks peroxidation of phospholipids of neuronal membranes. Along with that, ebselen protects cells from peroxynitrate which is formed with the participation of NO, glutamate toxicity, and slows down apoptosis processes in ischemic brain tissue. It significantly improves the state of animals in simulation of transient and permanent focal brain ischemia, and in the clinic it has already proved its effectiveness in ischemic stroke patients.

In experiment and clinical practice, the original Russian antioxidant mexidol which is a derivative of 3-oxypyridine succinate has been well-proven. The spectrum of its pharmacological activity is quite wide and includes anxiolytic and anticonvulsant action in addition to its nootropic effect. As an inhibitor of free radical processes, mexidol activates superoxide dismutase, suppresses LPO reactions, increases the concentration of reduced glutathione in cells, increases the content of phosphatidylserine and phosphatidylinositol in biomembranes due to its effect on their physical and chemical properties, and it reduces viscosity and increases fluidity of the lipid bilayer of neuronal membranes. The drug has also been found to modulate the activity of membrane-bound enzymes, ionic and metabotropic receptor complexes (glutamate, GABA-benzodiazepine, acetylcholine). By normalizing the blood rheological properties and by weakening the platelet aggregation, it further improves the cerebral blood flow.

Mexidol has already found application in clinics in cognitive disorders (memory, attention), decreased mental performance in elderly people and in those who had a stroke or a traumatic brain injury. The drug also turned effective in dyscirculatory encephalopathy and vegetovascular dystonia. In addition, the first clinical studies have confirmed good tolerability of mexidol and the absence of significant adverse reactions.

Beside the above mentioned compounds, the NO synthase (NOS) blocker nitro-L-arginine, some glutamate receptor antagonists (riluzole) and calcium ions (nimodopine), and nerve growth factor were found to have antioxidant properties to some extent too. In chemiluminescent model systems that generate reactive oxygen intermediates, piracetam, inferior in activity to mexidol, was nevertheless also able to exhibit a protective effect. The hormonal nootropic semax successfully suppressed LPO reactions in the ischemic brain. All this can be regarded as evidence of the prevalence of antioxidant properties and a possibility of pharmacological inhibition of oxidative stress manifestations as a part of nootropic activity.

This assumption is entirely true for the epiphyseal hormone melatonin, which we take to be a natural enhancer of cognitive activity. Probably, it currently attracts increased interest among clinical physicians not least due to its antioxidant properties.

In particular, it turned out that melatonin can serve as a ‘trap’ for free radicals due to its successful reaction with different kinds of highly toxic radicals (NO, singlet oxygen, hydrogen peroxide), thus it effectively protects neurons from oxidative damage. Due to unique physical and chemical properties of the hormone and its metabolites (e.g., 6-oxymelatonin), their action is comparable with some of the well-known antioxidants in terms of reliability and stability.

Melatonin inhibition of LPO described in vivo and in vitro in animals of various species is facilitated by the activating effect on superoxide dismutase and catalase as well as enzymes which are involved in the formation of another natural antioxidant, glutathione (glutathione peroxidase, glutathione reductase). At the same time, melatonin can inhibit enzymes with antioxidant properties (NOS, lipoxygenase) without a risk of inducing pro-oxidant effect. The direct involvement of the hormone in the fight against free-radical processes is supported by the fact that this action does not depend on the existence of specific

melatonin receptors.

The oxidative properties of melatonin appear to be directly related to an improvement of cognitive functions. Thus, injection of streptozotocin into the brain ventricles, which induces oxidative stress with the generation of large amounts of free radicals, provoked learning and memory disturbances in the simulation of avoidant behavior in rats. Concomitant chronic administration of melatonin eliminated mnestic disturbances with an increase in the level of malonic aldehyde in brain tissue. If galactose, which can reduce superoxide dismutase and glutathione peroxidase activity, caused amnesia with impaired active avoidance and spatial memory in the water maze in mice, than the epiphyseal hormone prevented negative biochemical and behavioral shifts.

Thus, available data leave no doubt that the ability to block free-radical processes, which is found in certain nootropics, is most directly related to the origin of their specific psychotropic activity.

28. Question: Is the stimulation of the central cholinergic transmission a mandatory component of the nootropic action?

Answer: Such framing of the question is quite valid. Indeed, today the leading position of the brain cholinergic mechanisms in the organization of cognitive activity is undeniable, and their dysfunction is considered to be the most important source of cognitive disorders.

Pharmacological assistance with the function of cholinergic synapses aimed at producing the nootropic effect can come off in different ways: limitation of the destruction of natural acetylcholine through inhibition of acetylcholinesterase activity, stimulation of pre- and postsynaptic cholinoreceptors, and enhancement the mediator synthesis. The first, time-proved way involves the use of acetylcholinesterase inhibitors. Physostigmine used to be the most popular among them, but in recent years it has been overshadowed by new, more effective compounds that also have less pronounced side effects.

In full accordance with the modern understanding of the role of cholinergic mechanisms in cognitive activity, the use of anticholinesterase agents induces predictable behavioral and neurochemical shifts in the experiment. They are manifested in faster development of conditioned responses in animals and improvement of various types of memory, which at the neuronal level is expressed in the form of easier induction and prolongation of long-term potentiation and a clear inhibition of amnesia caused by damage to cholinergic pathways or by M-cholinoblockers. With systemic or intracerebral administration of the substances, an accumulation of extracellular acetylcholine and an increase in its synthesis are noted, primarily in the neocortex and in limbic structures (hippocampus, amygdala), which negatively correlates with the content of the tissue and plasma acetylcholinesterase.

In clinical practice, acetylcholinesterase inhibitors have proven themselves in the treatment of cognitive disorders of organic nature, and they have taken a solid place in the range of drugs used to combat neurodegenerative diseases, especially Alzheimer's, due to their ability to alleviate intellectual and mnestic disorders.

Since the therapy of Alzheimer's disease, for example, requires a long-term and repeated prescription of substances, perhaps the most solid experience has been gained in the use of anticholinesterase drugs. In 1981 physostigmine was replaced by tacrine which proved to be very promising, and it was followed by amiridine, rivastigmine (exelon), donepezil (aricept), and others. Among them, tacrine, given its obvious advantages, now increasingly receives the palm of victory. However, the effectiveness of anticholinesterases in a neurodegenerative pathology when cholinergic neurons die, is not entirely clear. Indeed, sometimes their activity is variable and weakly expressed in severe, critical cases of the disease. Despite that, in general, the drugs are considered to be perhaps the most reliable ones, and this has a number of explanations.

It is likely that some of them, in addition to enzyme inhibition, can directly stimulate choline receptors and even inhibit apoptosis in the nerve cell culture. We cannot rule out the involvement of other neurotransmitter systems in their action as well. In particular, tacrine and rivastigmine increase the level of striatal dopamine, which seems to trigger the alleviation of not only cognitive but also motor disorders in parkinson's patients. Both drugs also enhance the function of NMDA receptors, acting as glutamate agonists.

Along with indirect stimulators of cholinergic synapses, the therapeutic effect can be achieved using substances with M-cholinomimetic properties. But while direct agonists of post- and presynaptic (M1 and M3) choline receptors do not yet meet the requirements of clinicians according to a number of criteria, there are quite promising nootropics that enhance the synthesis of acetylcholine from its precursors. These include gliatimine and citicoline.

The first one, being a derivative of choline, is transformed in the body into phosphorylcholine which improves the condition of neuronal membranes whose degradation is of particular importance in the pathogenesis of neurodegenerative diseases. Citicoline (cytidine 5-diphosphocholine) also serves as an intermediate product in the synthesis of membrane phospholipids. In resorptive administration, it breaks down into cytidine and choline. Simultaneously with improving cholinergic transmission, citicoline enhances the formation of other mediators (dopamine, noradrenaline), attenuating manifestations of tissue hypoxia and ischemia. Both substances have been successfully used over the past decade in cognitive disorders of various etiology (cerebral vascular diseases, traumatic brain injury, neurodegenerative pathology).

If the mechanism of elimination of cholinergic deficit and concomitant cognitive disorders by the substances described above is obvious, the existence of cholinomimetic properties in the pyrrolidone nootropics appears somewhat less certain. Does an enhancement of cholinergic transmission play any role in their specific action? And if it does, what role is that? Although the first part of this question has been repeatedly debated, the answer should probably be positive.

There is ample evidence of a close interaction between various racetams and cholinergic agents. Thus piracetam, oxiracetam and aniracetam, when administered systemically, prevented or attenuated behavioral disorders caused by scopolamine, improving behavior and memory in different animal models. While scopolamine reduced glucose utilization in various regions of the neocortex and in the dendritic neuropil of the CA1 and

CA3 fields of the hippocampus, piracetam eliminated this type of metabolic defect. Secoverine, which is a blocker of presynaptic auto-regulatory M-cholinoreceptors, improved the performance of mice in the passive avoidance test by enhancing the release of acetylcholine, which was potentiated by oxiracetam. The latter markedly enhanced the effect of nicotine in the same behavioral model.

Another, in our opinion, quite remarkable fact, also obtained in the use of oxiracetam, deserves attention. It clearly attenuated scopolamine amnesia in rats during the training of the conditionally reflexive passive avoidance reaction. However, when the nootropic dose was increased (from 30 to 100 mg/kg), its protective effect disappeared. This observation once again points to the absence of an oftentimes linear dose-effect dependence after an administration of some nootropic agents.

The stated facts provide clear evidence for the involvement of cholinergic mechanisms in the nootropic activity of racetams. However, we cannot yet speak of the direct involvement of the cholinergic system based on that, since the described synergy could also be formed outside of this system. Direct arguments in favor of the stated position are nevertheless presented in a number of papers.

It was found that nefiracetam, while weakening the amnesia caused by a damage to the forebrain base or by scopolamine, simultaneously increased the release of acetylcholine in the brain. Restoration by this substance of spatial and working memory in rats during passive avoidance training correlated with an increase in choline acetyltransferase activity in the hippocampus. An improvement of active avoidance learning in old but not young rats under the influence of piracetam was accompanied by an increase in the cortical and striatal M-cholinoreceptor density and an increase in high-affinity choline uptake in striatum and hippocampal slices. Thus, direct evidence for the mobilization of cholinergic neurons by pyrrolidone type nootropics was obtained, although the underlying mechanisms still remain unclear.

A cholinergic component is also present in the action of some other nootropic agents. For example, substances that enhance glutamatergic transmission may possess cholinomimetic activity. D-cycloserine as a stimulator of the glycine site within the NMDA receptor clearly attenuates scopolamine amnesia in the model of passive avoidance; and primary components of the plant nootropic Ginkgo biloba eliminated a former decrease in the hippocampal choline acetyltransferase activity in parallel with the reduction of mnestic disturbances.

It is worth noting that the experiment also provides evidence for a connection between the nootropic properties of neurotrophic factors and the triggering of cholinergic mechanisms. Intracerebral administration of NGF, in particular, eliminated memory and learning deficits in rats with damaged cortex and markedly increased the content of acetylcholine in the hippocampus. On the other hand, the activation of H-cholinergic synapses by nicotinic receptor agonists successfully regulates the gene expression of, for example, fibroblast growth factor (FGF), which explains their effectiveness in the treatment of Alzheimer's disease and parkinsonism.

As it follows from the above information, the pharmacological profile of nootropic

drugs of different origin, not only traditional anticholinesterase compounds, includes a fairly distinct cholinergic component. Therefore, the above question requires an affirmative answer, and this circumstance shall be taken into account when describing their specific activity.

29. Question: Do the dopaminergic mechanisms of the corpus striatum take part in the specific activity of nootropics?

Answer: If we judge by the role of the striatum in the processes of higher nervous activity, there is every reason to answer affirmatively. However, as with other neurotransmitter systems of the brain, the answer cannot be unambiguous.

The probable contribution of cerebral dopaminergic and, in particular, nigrostriatal mechanisms to the nootropic effect has repeatedly been the subject of study; but results, at first glance, appeared to be inconsistent. With that said, a smaller proportion of the data seemed to tell against their interest in the pharmacological response.

A number of observations show that piracetam and its derivatives (oxiracetam, pramiracetam) do not significantly impact the content of the striatal dopamine determined by microdialysis; the mediator level also does not change when the substances are added to the medium where the striatal sections are incubated. A similar negative result was obtained in experiments using vinpocetine. Furthermore nefiracetam and glutamate-originated nooglutil did not alter the binding of striatal D1- and D2-dopamine receptors to specific ligands, and piracetam and clofenoxate were ineffective in a model of circling behavior provoked by intrastriatal dopamine injection; hence we can easily conclude that nootropic agents do not interfere with dopaminergic transmission.

However, such a conclusion would be hasty for two reasons. First, in the cited papers, with direct determination of dopamine concentration in the striatum only the absolute values of the index fail to change. But the function of the dopaminergic synapses is still subject to drug modulation since the authors often found accumulation of the main dopamine metabolites in the nucleus, namely homovanillic and dioxyphenylacetic acids. And this is a sign of increased turnover of the mediator. Secondly, the given facts were obtained in healthy animals, without simulating any pathological conditions.

Meanwhile there is a more representative group of studies according to which nootropics can still increase accumulation of striatal dopamine. In rat striatal slices, even low doses of piracetam increase the potassium-stimulated release of the mediator, and in striatal homogenates its content increases simultaneously with a decrease in serotonin levels. Nooglutil did not have an effect on the parameters of the labeled spiperone ligand binding to D2 dopamine receptors in striatum sections in vitro, but in vivo it increased the number of such receptors and their ligand affinity. In spontaneously hypertensive, stroke-prone rats, a decrease in the basal dopamine and serotonin content was found in the striatum, amygdala, hippocampus, and prefrontal cortex. And regular, preventive use of aniracetam eliminated such a defect and markedly increased the monoamine release. While in intact rats neither piracetam nor tacrine significantly changed the content of these transmitters, in thymectomized animals on the other hand the level of striatal dopamine and its metabolites

increased. Antagonism of piracetam and aniracetam with the dopamine receptor blocker haloperidol has also been described in different models. In old, but not young rats, for example, aniracetam shortened the immobilization time in the dynamics of the swimming behavior due to its dopamine mimetic effect, and the neuroleptic easily suppressed this effect of the nootropic drug.

A particularly clear stimulating effect of nootropic agents on dopaminergic transmission is revealed against the background of experimental simulated ischemic and hypoxic brain conditions. For example, the exposure of striatal slices to hypoxic environments or a simulation of hemorrhagic stroke inhibit dopamine release, but such disturbances are reliably attenuated by piracetam. When the cerebral ischemia was induced by blocking the small vessels with microspheres, there was a decrease in the concentration of dopamine in the striatum and serotonin in the hippocampus. A repeated administration of a new nootropic agent nebracetam partially eliminated the emerging neurotransmitter disorders. Nefiracetam clearly limited mnestic disturbances and a decline in the dopamine turnover in the striatum and frontal cortex caused by an intraventricular injection of the beta-amyloid peptide which is attributed an important role in the origin of Alzheimer's disease.

The given data undeniably prove the ability of nootropics to improve nigrostriatal dopaminergic transmission, especially against the background of its previous impairment; and they refer mainly to pyrrolidone derivatives. Meanwhile, there are convincing arguments that other nootropics which differ significantly in their origin, can also have a similar effect. Thus, citicoline, which limits cognitive impairment in cerebral ischemia, increased the release of dopamine through the stimulation of the enzyme tyrosine hydroxylase of nigrostriatal neurons. The original Russian drug Phenibut that has nootropic and anxiolytic properties was found to have an activating effect on postsynaptic dopamine receptors, and an herbal nootropic derived from hypericum reduced the binding of labeled spiperone to D2-receptors in the rat striatum.

Cognition-enhancing hormone medications also exhibit dopamine mimetic activity. In the epiphyseal hormone melatonin it comes down to the protection of nigrostriatal dopaminergic neurons from degeneration caused by various neurotoxins (6-OHDA, MPP), whereas the ACTH 4-10 drug semax limited the death of cells in the substantia nigra, caused by systemic administration of another cell-damaging compound - MPTP. Along with that semax normalized the synaptic function of the surviving nigral elements, and eliminated motor and behavioral disorders that accompany intoxication.

To sum things up, we need to place on record that the substances which are very different from each other in origin and, obviously, in the spectrum of cellular action are nevertheless somehow capable of restoring the nigrostriatal restraining control of the work of the striatum which is disturbed under pathological conditions. Taking into account the participation of this brain structure in the organization of behavior and cognitive processes, the indicated neurotransmitter shift shall serve, among other things, as an indispensable element of the nootropic effect. Also it shall not go unnoticed that psychomotor stimulants of the amphetamine group have similar properties, therefore an enhancement of the dopaminergic transmission can be a source of additional psychostimulatory activity of

nootropics.

Of course, an activating effect of nootropics on the function of nigrostriatal dopaminergic synapses is not isolated. Other projection tracts where dopamine is also a transmitter, are bound to be involved in their action. These primarily include tracts ascending from the midbrain to the anterior neocortex and limbic nuclei. However, the fact that dopaminergic mechanisms of the striatum specifically are involved in the response to nootropics is not only convincingly substantiated today, but there is reason to believe that the execution of their activity directly depends on it.

Since the nootropic agents sometimes have ambiguous effects (stimulating or depressing) in relation to individual neurotransmitter systems depending on their functional state (a typical example is glutamatergic synapses), it is reasonable to expect similar duality of their effect on the dopaminergic transmission. If, against the background of its hypoactivity, they produce a stimulating effect, do they lead to the opposite shift in case of the initial hyperfunction of the system?

The question looks quite valid. It is possible that due to this reason nootropic agents limit cognitive impairment in schizophrenic patients and the severity of stereotypic behavior in animals. In psychiatric practice, they often appear to be synergists of neuroleptic dopamine blockers whose efficacy in such a combination can significantly increase in pharmacoresistant cases. Indications that piracetam and aniracetam can, under certain circumstances, decrease the content and turnover of monoamines in the striatum can be considered a neurochemical justification for the synergism.

30. Question: What is the nature of GABA-eric compounds as nootropics?

Answer: Based on the important role of GABA in the organization of cognitive processes, such substances should have an essential place among nootropics. However, this is not exactly a universal statement. First of all, this is due to an unusually diverse composition of the GABA-mimetics group. They include GABA itself in the form of aminalone (gammalone), its cyclic derivative from the racetam family - piracetam, and some compounds related to it, complexes of GABA with vitamins - pantothenic (pantogam) and nicotinic (picamilon) acids, sodium oxybutyrate, phenibut. On the other hand, these agents have an extremely wide spectrum of pharmacological activity which includes anti-amnesic, anti-hypoxic, anxiolytic, sedative, and anticonvulsant properties. Since for some GABA-mimetics the nootropic effect is not a determining one but it only accompanies other specific effects (a typical example is GABA-mimetic anticonvulsants such as sodium valproate or carbamazepine), it is proposed to consider them as substances with a mixed (‘non-genuine’) nootropic activity.

Piracetam belongs to the most popular representatives of this group, which have been used for a long time, but not yet fully studied. Even though it is a cyclic analogue of GABA, it is only partially converted into a linear form of the amino acid when it enters the body. Nevertheless, the set of properties of piracetam is very similar to that of aminalone, which makes it a typical GABA-mimetic. There are several other aspects that bring them together.

To reveal the effect of these substances on cognitive functions, there has to be (as in the case of most other nootropics) the initial organic mental insufficiency, the need for long-term therapy and besides that with rather high doses of the substances. And we have to admit that other GABA-mimetics are clearly inferior in their nootropic activity.

The components of an anti-amnesic action of the substances from the GABA group are very diverse. Obviously, in order of importance the first place shall go to the metabolic and vasodilatory properties of GABA-mimetics which determine their antihypoxic action, especially in conditions of preceding brain ischemia. While the cerebrovascular insufficiency was simulated by hypokinesia and chronic stress, even a single injection of piracetam or aminalon against such a background was accompanied by a marked increase in the average diameter of brain capillaries and a reduction in the number of sharply narrowed vessels, there was a dilation not only of arteries, but also of veins, even though perivascular edema changed insignificantly. A relief of ischemic manifestations coincided with normalization of cognitive processes.

Even in total cerebral ischemia after bilateral carotid artery occlusion, piracetam and xanthinol nicotinate provided a protective effect, significantly reducing animal mortality in the late terms of reperfusion. It can be noted that an increase in the GABA content in the cerebrospinal fluid of patients in the first hours after an acute stroke can be considered as an indicator of the triggering of the natural protective mechanism aimed at fighting hypoxia.

Of course, synaptotropic properties of GABA and its preparations must be directly interested in the anti-amnesic effect, as long as the deterioration of cognitive activity is associated with a violation of the function of GABA-ergic mechanisms of the brain. This depends on the weakening of the inhibitory mediator role of the amino acid in the center and in the periphery; and there are several therapeutic mechanisms for the fulfillment of this role.

The inhibitory GABAergic neurons in the area of ischemic brain damage have a protective mission. Restricting the activity of nerve cells shall secondarily reduce their need for oxygen and nutrients thereby increasing their resistance to hypoxia. In addition, the neurotoxic effect of an excess of certain transmitters is reduced. Hyperpolarization of the cell membranes under the influence of GABA prevents excessive depolarization provoked by EAA and glutamate, in particular. The weakening of the demand for oxygen and the glutamate-calcium cascade is particularly important for the vital activity of cells in the ischemic ‘penumbra’ in acute disorders of the cerebral circulation in case of stroke or traumatic brain injury. This allows to delay further progression of the necrotic process and sometimes even reverse it.

The restoration of the mediator role of the amino acid by means of GABA-mimetics will definitely contribute to normalization of synaptic plasticity in the hippocampus, striatum, cortex and other brain formations actively involved in the organization of the higher nervous activity. This can be based on increasing effectiveness of inter-neuronal interaction and improvement of integration and coordination processes carried out by means of short-axon GABAergic interneurons.

At the same time, it is important to restore the function of GABAergic projection tracts, which innervate the leading cognitive structures in close cooperation with cholinergic and

glutamatergic cells. It is believed that inclusion of long-axon GABAergic neurons in the septo-hippocampal projections and tracts ascending from the base of the forebrain to the neocortex (damaged, incidentally, in Alzheimer's disease) is one of the main reasons for attenuation of mnestic disturbances in humans and animals by substances.

The synaptic role of GABAergic mechanisms turns out to be impaired in aging. For example, defects in the functioning of GABA and glutamate transporters were found in synaptosomes isolated from the cortex of old but not young rats. Application of GABA and muscimol to cortical neurons of old monkeys induced potentials with lower amplitude compared with young animals. The effect of GABA receptor antagonist bicuculline was also evident in the aging brain. At the same time, against the background of repeated systemic injections of GABA, the age-related difference in GABA cell reactivity was leveled out noticeably.

Another factor contributing to the optimizing effect of GABA-mimetic agents on the brain may lie in the synchronization of oscillatory processes in the body, if dysrhythmia is considered a condition favorable for cognitive disorders. In humans, manifestations of rhythm-stabilizing effects of GABAergic agents include normalization of nighttime sleep and emotional status and weakening of depressive symptoms; and in animals it is the formation of more distinct biological rhythms of different periods. Similar chronobiological shifts accompany the use of benzodiazepine derivatives with their stimulating effect on GABA-benzodiazepine receptor complexes. Based on this understanding of the problem, it is reasonable to consider the anticonvulsant properties of different types of GABAergic agents combining nootropic and anticonvulsant effects, as an indicator of elimination of motor dysrhythmia. A basis for synchronization of the circadian rhythm can be an enhancement by GABA-mimetics of inhibitory control of the leading pace-maker mechanism - the suprachiasmatic nuclei of hypothalamus, an increase of melatonin secretion by epiphysis, as well as the limitation of hyperactivity of hippocampal neurons.

The therapeutic effect of GABA-mimetics in cerebral pathology can be contributed by an improvement of the light and color perception function of the eyes. The weakening of the visual perception regularly accompanies aging and even serves as a diagnostic criterion of the deterioration of the brain activity in traumas and neurodegenerative diseases. Cerebral pathology adversely affects the functional state of the retinal photoreceptor apparatus, primarily because of the local weakening of hemodynamics as well as synaptotropic properties of GABA. In this regard, it is curious that ischemic phenomena, as a rule, are accompanied by an increase in the level of retinal GABA as a kind of protective reaction. According to our observations, piracetam has the ability to improve light and color perception in persons who have suffered a traumatic brain injury, by significantly reducing the thresholds of the retinal brightness sensitivity.

Local normalization of GABAergic processes and blood circulation in the retina itself, as well as pharmacological modulation of the activity of the central parts of the visual analyzer can be the reason for an improvement of the visual function. Intrinsically, according to ophthalmoscopy data, in humans with dyscirculatory encephalopathy piracetam increased the blood filling of retinal vessels and optimized visual spatial object recognition. And in

animals, after an administration of the GABA-mimetic muscimol or piracetam, some characteristics of the unitary activity of the visual cortex neurons on light signals were altered.

Hence, there are various prerequisites for ensuring the nootropic effect with GABAergic agents. At the same time, as already noted, some representatives of this pharmacological class also have other therapeutically valuable properties (anticonvulsant, muscle relaxant, sedative, anxiolytic, etc.), which in clinical practice push their nootropic activity aside.

31. Question: To what extent are the ovarium estrogenic hormones in charge of cognition?

Answer: As already noted, almost all hormones impact memory and learning processes to a greater or lesser degree. Among them, ovarian estrogens probably stand out due to their particularly pronounced psychotropic activity.

This state of matter was evidently confirmed by our earlier analysis of the results of a large number of studies. It points at the ability of both the estrogenic hormones themselves and the gonadotropins that regulate their secretion, to interfere with metabolism and synaptic transmission in various brain structures. In experiments on animals this is accompanied by reorganization of not only sexual, but also conditioned reflex behavior. In particular, the processes of perception and attention, short- and long-term memory, motor and sleep can alter. Mobilization of specific estrogen receptors which are identified in rostral brain formations, leads to changes in the functional state of the neocortex, striatum, and subcortical limbic nuclei. According to the facts given at that time, the mentioned shifts were explained by the predominant influence of estrogens on the central dopaminergic mechanisms and to a lesser extent on noradrenaline-, serotonin-, and GABA-ergic mechanisms.

In recent years, the above statements have been clarified and supplemented, including with respect to the mnestic properties of the hormones. It has been found that in healthy women not all types of memory are equally dependent on the level of plasma estrogens. Its level has a weaker effect on spatial memory and a much stronger effect on episodic and verbal working memory. The latter is also more easily restored in postmenopausal women with estradiol injections.

The activation of cognitive processes with ovarian hormones is normally associated, among other things, with an increase in the information inflow to central neurons, especially due to the activation of cholinergic mechanisms. Thus, the combined use of estrogens and gestagens (combination drug climodien) markedly increases the amplitude of evoked auditory potentials in the cortex of female monkeys, and the prolonged estrogen administration eliminates the deficit of the visual-spatial attention in ovariectomized animals. After ovariectomy, the hormones also attenuated visual disturbances caused by the M-cholinoblocker scopolamine.

The last fact underlines the essential point that hormone-induced changes in the cognitive sphere are largely of cholinergic origin and are associated with a launch of the

system of forebrain base neurons. In particular, the removal of the gonads markedly impacts the activity of acetylcholinesterase in various brain structures. According to microdialysis data, in pre-ovariectomized rats who received estradiol for several weeks, potassium-stimulated acetylcholine release increases dramatically in hippocampal slices.

Significant attention is now paid to the involvement of estrogens in the genesis of various types of organic mental insufficiency and mechanisms of their compensation. Hormone deficiency explains, for example, gross abnormalities in the spatial working memory test in aging female monkeys. Cyclic administration of low doses of estradiol to them improved the performance of mnestic tasks, whereas ovariectomy clearly aggravated disorders in discrimination learning. While global ischemia caused the death of neurons in the CA1 field of the hippocampus, steroidal and nonsteroidal estrogens (estrone, estradiol, diethylstilbestrol) protected pyramidal cells from the ischemic damage and improved the learning in post-damage female animals. Insufficient production of estrogenic hormones or a disturbance of the rhythm of their normal secretion also determines the development of the depressive syndrome in women, which is accompanied by various kinds of cognitive disorders.

The deficiency of estrogen's neuroprotective and anti-degenerative function is probably one of the reasons why organic brain lesions develop more easily. Taking into account the frequent occurrence of a neurodegenerative pathology in the form of Alzheimer's disease in elderly women, the problem of its pathogenetic connection to estrogenic insufficiency is extremely urgent nowadays. A natural decline in the plasma concentration of hormones in the postmenopausal period is considered to be perhaps the most dangerous risk factor for unleashing this disease with a typical combination of cognitive disorders and neurodegeneration, primarily in brain areas that contain cholinergic neuron bodies. At the same time estrogen replacement therapy in older women markedly reduces the risk and delays the onset of Alzheimer's disease (Gilman S., 1997).

However, this problem cannot be considered conclusively solved because of the contradictory findings of some researchers, some of whom cast doubt on this correlation. They claim that the treatment with estrogenic hormones does not provide reliable shifts in the clinical dynamics of Alzheimer-type dementia. However, in this case, obviously we shall rather speak about a moderate to severe pathological process caused by an overly pronounced and far aggravated neurodegeneration. Assumably, there is a sort of critical window for more successful use of estrogens, when their protective effect is at its maximum. Therefore, it is advisable to begin the therapy as early as possible, at the first signs of the disease, i.e. soon after the onset of the postmenopausal period.

In our opinion, there is a reason behind this quite rational approach, according to which not the beta-amyloid peptide itself, but its precursor can serve as a target for estrogens. This is evidenced by the low content of the latter in the blood of women who received estradiol for a prolonged period of time. The inhibition of the formation of toxic amyloid, combined with the antioxidant properties of estrogen undoubtedly serves as an important preventive measure against Alzheimer's disease.

In addition to inhibiting the amyloid intoxication, ovarian hormones can also protect

nerve cells from destruction in other ways. One mode of protection is the inhibition of apoptosis. In particular, an injection of 17-beta-estradiol into the medium where hippocampal and septal cells were incubated, reduced the extent and slowed down the rate of aziridine-induced cell death. This may be due to expression of estrogenic alpha-type receptors and induction of the anti-apoptotic protein Bcl. This kind of neuroprotective activity of the hormone was blocked by its antagonist tamoxifen. Along with that, the necrotic cell death associated with excess glutamate or oxygen and glucose deprivation, was not attenuated by estradiol. It could provide neuroprotection in stroke and cerebral ischemia through the activation of protein kinase C which plays a key role in the regulation of apoptosis.

A stimulating effect on the synthesis of neurotrophic factors such as the nerve growth factor, which is shown in estradiol also undoubtedly leads to the protection of nerve cells from degeneration. The development of dendrites is regulated by switching on the membrane receptors of estrogen and further forming a cAMP-sensitive nuclear effect. Incidentally, the activation of such membrane receptors, rather than classical nuclear receptors, provides urgent, nongenomic cell responses to estrogens. Among other things, they help to attenuate the potassium current in the hippocampal pyramids and increase neuronal excitability.

The anti-inflammatory properties of hormones can be interested in estrogenic neuroprotection. Thus, systemic administration of 17-beta-estradiol prevented microglia activation and lipopolysaccharide-induced increase in the number of monocytes in peripheral blood. The restriction of hormonal expression of anti-inflammatory factors did not occur when the drug was administered to mutant mice devoid of alpha- but not beta-estrogen receptors.

In addition to the said mechanisms, ovarian estrogens can attenuate cognitive impairment in other ways, including by regulating the synaptic inflow of information to neurons. Hormone deprivation initiates or increases degenerative changes in nerve cells, caused by oxidative stress because of impaired synaptic plasticity, primarily in the cholinergic pathways. A prolonged decrease in ovarian function weakens cholinergic transmission and negatively affects the expression of neurotrophins and tyrosine-kinase mRNA receptors. In contrast, injections of estrogens or estradiol-progesterone complex, in parallel with increased choline acetyltransferase activity and increased acetylcholine release, also normalized the learning in animals, eliminating amnesia. However, similar to severe cases of Alzheimer's disease, ovariectomy in old rats causes such severe lesions of cholinergic mechanisms in the septum and base of the forebrain, that they cannot be subsequently compensated by the administration of exogenous estrogens.

In addition to restoring cholinergic transmission, estrogens can probably also modulate the function of glutamatergic synapses. In ovariectomized mice repeatedly treated with estrogen, the competitive NMDA receptor antagonist CPP impaired the spatial learning in the water maze more weakly compared to those without hormonal protection. An addition of CPP to hippocampal slices in combination with estrogen also far less severely inhibited the long-term potentiation. Based on such facts, it is reasonable to assume that estrogens, among other things, can increase the number of active NMDA receptors in the hippocampus.

Therefore, summarizing the above data, we can state that the ovarian estrogenic hormones have quite a distinct nootropic activity. These properties of estrogens are better manifested in conditions of cognitive pathology, but sometimes they are weakly expressed or non-existent against the background of severe neurodegenerative changes of cerebral neurons.

32. Question: Can the epiphyseal hormone melatonin be considered as a potential nootropic?

Answer: Among other hormones, it is probably the most justified one in claiming to be a natural nootropic due to a number of objective reasons.

The functional significance of the epiphysis as a source of melatonin has long been confined mainly to the organization of oscillatory processes in the body, in particular, diurnal periodism. Normal secretion of the hormone by the gland is regulated by the clear circadian rhythm, with a maximum in the dark and minimum in the light period of the day. Since it is connected with the visual apparatus through the driver of circadian biorhythms, the suprachiasmatic nuclei of the hypothalamus, the epiphysis adjusts the work of the brain and peripheral organs to the periodic change of external illumination with the help of melatonin.

However, this overly one-sided view of the role of epiphysis has now been reconsidered. Under the weight of many factors, researchers have been forced to admit that the gland has a much richer palette of functional properties. Due to the discovery of melatonin's ability to control various biochemical processes through different mechanisms, a concept was formed according to which the epiphysis has been given an important place in the brain protection system against all kinds of negative influences, including those of a stressor nature. And it is quite significant that the components of stress-protective activity of melatonin largely coincide with the effects of traditional nootropic agents.

Nootropics, for example, are known to limit excessive processes of apoptosis. A similar activity has been shown in melatonin. In the primary culture of rat cortical neurons, when apoptosis was simulated by ischemia or aziridine, the addition of the hormone to the medium provided a reliable anti-apoptotic effect. Melatonin also protected dopaminergic neurons of substantia nigra from ‘programmed death’, which explains its therapeutic potential in parkinsonism.

The immune mechanisms are of significant importance in the system of neuroprotection, on the one hand, and neuronal damage, on the other hand. And melatonin has been shown to have distinct immunomodulatory properties. By direct or indirect involvement in the function of immune-competent cells, it can enhance the immune reactivity when it is restricted, demonstrating immunostimulatory capabilities. And against the background of an increased immune response, the hormone, on the contrary, can provide an immunosuppressive effect. Due to such immunomodulatory activity, it is recommended for use in autoimmune and oncological pathologies. Naturally, such properties cannot but be in demand in the process of organization of the cognitive activity as well.

The hormone has also been shown to have antioxidant activity. It is capable of limiting

oxidative stress, acting as a ‘trap’ for free radicals and as an activator of glutathione formation.

On top of the above, there is also quite some evidence for a direct effect of melatonin through specific receptors which are widely present in the brain, on structures that are associated with the formation of memory, in particular on the hippocampus. Its direct interest in the effects of the hormone is evidenced, among other things, by the results of our studies. Limited hippocampal disruption prevented the hormone from influencing the behavior of rats in a conflict situation, whereas a specific theta rhythm in the hippocampal EEG changed in the opposite direction when melatonin was introduced and epiphysis was removed, with a clear time-of-day dependence. The addition of the hormone to the medium with hippocampal slices induced a two-phase change in the amplitude of evoked electrical responses, whereas melatonin microinjections into the CA1 field in rats were reflected in the duration of post-tetanic potentiation and spatial learning of animals.

It is assumed that the effect of melatonin on memory may be due to its ability to increase the expression in the hippocampus and neocortex of a special kind of neural cell adhesion molecules (NCAM) from the family of immunoglobulins involved in central synaptic transmission and in memory processes. At the same time, a decrease in the melatonin level in the cerebrospinal fluid is offered as an explanation of the high functional vulnerability of brain structures of the so-called hippocampal circle (entorhinal cortex - hippocampus - septum - mammillary bodies) in people suffering from Alzheimer's disease.

Along with that, melatonin is actively involved in the control of perceptual processes, primarily by regulating the activity of the visual analyzer. It is widely present in the retina where it modulates its light sensitivity, and for this reason it can increase the photoreceptive function of the eye as evidenced by a decrease of the threshold of visual perception in humans after taking the hormone. In addition, high density of melatonin-specific binding sites has been shown in the antero-ventral and antero-dorsal nuclei of the thalamus, which have direct connections with the retinal elements and are simultaneously involved in the learning and mnestic processes.

The summary of the above evidence leaves no doubt that epiphyseal melatonin shall be directly interested in the organization of cognitive activity. Nevertheless, there is a group of observations which, at first sight, seem to contradict this conclusion. As it is established in experiments on rats, while raising the threshold of electroshock convulsions, melatonin (50 mg/kg) did not improve, but on the contrary, impaired the animals' memory for a long time. Its use in considerable doses (up to 100 mg/kg!) sharply impaired short-term memory and learning in the elevated plus maze. Fairly representative data are shown in healthy humans, in carefully controlled studies using various sets of cognitive tests, according to which repeated administration of melatonin (1.5-3 mg) had no effect whatsoever on the speed and accuracy of performing the given tasks. Since determinations were made at the time of the rise in plasma hormone concentration, only a slight increase in response time was detected, which coincided with a decrease in body temperature typical for melatonin.

However, if we take into consideration a number of factors, it is hardly reasonable to speak about the contradiction of the above facts to the postulated concept of the nootropic

properties of melatonin. The point is, that both from the physiological and pharmacological points of view, its activity is characterized by an exceptional dependence on many variables (time of day, administration scheme, age and species of animal, etc.), primarily because of the peculiar modulating nature of the hormonal effect. Among these factors, perhaps of particular importance are the dose of the substance and the initial functional state of the body. In the cited experiments indicating the amnesic effect of melatonin, its inadequately high doses were used. The administration of more than 5-10 mg/kg of the hormone, in our opinion, simply makes no sense because it has no linear dose-effect dependence; besides, in large doses melatonin often causes shifts opposite to those induced by low doses.

In addition to the correct dosage, another circumstance of no less importance would be the understanding of the physiological role of the epiphysis. Without determining any specific functions, the gland only corrects the work of the brain and internal organs if this work falls outside the norm. That is why the epiphysis visibly reminds of its existence mainly under conditions of one or another functional disorders. For this reason the initially healthy and even more so young organism with a full-fledged production of the natural hormone simply cannot be responsive to it. Similar to traditional nootropic agents, the true potential of melatonin requires an underlying pathological disorder, and even more specifically, an organic cerebral defect. The following facts confirm the validity of this statement.

A short-term global brain ischemia which led to the death of hippocampal CA1 field neurons and impaired the learning and working memory in animals in the T-shaped maze, provoked less pronounced morphological and behavioral changes when carotid artery occlusion was preceded by melatonin administration. An ischemic edema as a model of stroke, according to nuclear magnetic resonance data, was accompanied by rough functional shifts in the new cortex and striatum. And in this case, the preliminary use of the hormone provided a protective effect better pronounced in the cortical area. Conversely, the epiphysis ectomy which by itself did not alter memory in rats, significantly potentiated its impairment in combination with a moderate cerebral ischemia, and such synergy was accompanied by a more significant drop in the number of pyramidal hippocampal neurons.

Melatonin also reveals the ability to eliminate amnesic disorders in various forms of neuro intoxication. In the case of intracerebral injections of aluminum chloride, memory deterioration was shown in the model of passive avoidance and orientation in the Morris water maze in mice. Chronic injection of the hormone improved orientational avoidance behavior simultaneously with an increase in previously reduced superoxide dismutase and glutathione peroxidase activity in the hippocampus and cortex. Under its influence the toxic effect of ochratoxin (a poison of some mushrooms, detected in food products) in relation to hippocampal NMDA-receptors was partially attenuated. But particularly curious, clinically important results were obtained when studying the neuroprotective properties of the hormone against the background of neurodegenerative processes caused by beta-amyloid peptide. Such neuro intoxication is taken as one of the leading pathogenetic links of Alzheimer's disease.

Bilateral intrahippocampal injection of beta-amyloid (Abeta 25-35) to rats, along with a sharp decrease in the number of nerve cells in the cortex and in the hippocampus itself, also caused severe cognitive disorders in the form of deterioration of passive avoidance reactions

and spatial orientation in the water maze. If the peptide was used in combination with a repeated administration of melatonin, pathomorphological shifts were clearly inhibited in parallel with improvements in memory and learning. Similar results were obtained in another experimental model of Alzheimer's disease - behavioral disorders resulting from chronic ethanol poisoning.

Experimental findings coincide with the results of still rare clinical observations. In patients with a pronounced form of this pathology, long-term (3-4 months) administration of melatonin (6 mg daily) led to an improvement of various parameters of sleep and cognitive functions. In this regard, there is an interesting clinical case where melatonin in combination with conventional pharmacotherapy was prescribed for a very long time (36 months) to one of the two homozygous twins who suffered from genetically determined Alzheimer's disease. In the end of the treatment course, the patient was found to have a milder form of the disease with a more pronounced improvement in memory compared with his twin. Shifts in the secretory activity of the epiphysis also explain rapid optimization of cognitive indicators in a neurodegenerative pathology (Alzheimer's and Parkinson's diseases) if patients were subjected to magnet therapy sessions with the use of low-intensity magnetic fields of the picotesla range.

Thus, there is now convincing proof of the existence of a distinct psychotropic activity of the epiphyseal melatonin, which is similar in its origin to the effects of traditional nootropic agents. The most convincing beneficial effect of the hormone on cognitive processes was demonstrated on experimental models of organic cerebral pathology, as well as in clinical conditions. All these facts suggest that, as a natural nootropic compound void of any side-effects, melatonin with its therapeutic potential is still underestimated by clinicians.

33. Question: What is the nature of neuropeptides as nootropics?

Answer: Neuropeptides of different origin definitely deserve to be referred to as very promising nootropics. They include peptide complexes (cerebrolysin, cytomedins), hormone-like compounds (semax, thyroliberin), synthetic peptide analogues (noopept), peptidase inhibitors.

Among the peptide drugs that differ significantly in composition and degree of trials in clinical conditions, in our opinion, Cerebrolysin stands out and must be ranked first in importance. It is a lipid-free complex derived from pig brain, 15% of it consists of a mixture of biologically active oligopeptides (with a molecular weight of no more than 10000 daltons) and 85% of free amino acids. Over a long period of use in neurological practice, Cerebrolysin has proven its clinical efficacy in the treatment of various forms of organic cerebral pathology (strokes, traumatic brain injuries).

However, since 1995, the interest in the drug has increased tremendously. This is due to the fact that the understanding of the mechanism of its cellular action, which turned out to be much more universal than previously thought, has been significantly expanded, and the scope of indications for use has been broadened. In particular, they now include a variety of dementia conditions. As it turned out, cerebrolysin significantly exceeds many nootropic

agents proposed for this purpose, in terms of its anti-dementia activity and its stability.

Cerebrolysin has revealed a surprisingly wide profile of neuroprotective properties, related to its ability to enhance cell regeneration processes and provide neuroprotection. First of all, it must be noted that it is the only preparation with a proven neurotrophic action, which has been reliably tested in the clinic. It is important that in relevant experimental models (spatial orientation, cerebral ischemia) it turned out to be significantly more active compared with the benchmark nerve growth factor (NGF) administered intracerebrally.

In addition, cerebrolysin prevents a decrease of the presence of the protein (MAP-2) associated with microtubules of neurons and normalizes the immune reactivity of another protein associated with synapse regeneration - synaptophysin. As a result, several effects are noted: restoration of the nerve cell cytoskeleton, preservation of nerve cell plasticity during acute and chronic damage, improvement of dendrite branching process, increase in the number of synaptic contacts. And such shifts correlated with elimination of disorders in spatial orientation and learning ability of animals in the water maze. The drug also has the ability to protect neurons from various neurotoxic factors: oxidative stress, glutamate hyperactivity, beta-amyloid peptide.

Cerebrolysin is also characterized by anti-apoptotic activity. Thus, its addition to the culture of cortical neurons under conditions of neurotrophin deprivation slowed down genetically programmed cell death, the same as in the zone of ischemic ‘penumbra’ surrounding the area of brain infarction. Besides, cerebrolysin increases the rate of GLUT-1 protein synthesis, which ensures the transport of glucose from blood to brain tissue through the blood-brain barrier, and which is decreased in Alzheimer's disease. Meanwhile, according to the positron emission tomography (PET) data, dementia is accompanied by a sharp decrease in the rate of glucose metabolism in the frontal and temporal lobes of the cortex. Lastly, cerebrolysin prevents pathological activation of microglia and attenuates the release of proinflammatory cytokines by glial cell elements. As a result, inflammatory reactions which play a significant role in the pathogenesis of neurodegenerative diseases, are limited.

The described properties explain the remarkable effectiveness of Cerebrolysin in the treatment of cognitive disorders accompanying organic mental insufficiency of different genesis. While acknowledging the obvious advantages of the drug, we must nevertheless point out one serious disadvantage. Like other peptides, it is easily destroyed in the gastrointestinal tract, and therefore is only suitable for parenteral administration.

Along with cerebrolysin, other peptide complexes are eligible for the therapy of cognitive pathology. The therapeutic properties of peptide extracts from various organs and tissues (thymus, liver, endocrine glands, etc.) have long been known. Despite their different origin, numerous preparations based on them (thymalin, hepalin, pancrealin, etc.) produce similar, in our opinion, nonspecific effects. These effects mainly come down to modulation of the immune response and increase in general reactivity of the organism. The active principles of such preparations, so far unidentified, are united by the general term cytomedins. Cytomedins include extracts from different cerebral tissues - cortexin (derived from gray matter) and epithalamin (epiphysis neuropeptide complex).

Unlike cortexin, epithalamin is well tested and has been successfully used in clinical

practice for several years. Its composition has not been finally deciphered, but it is obvious that it contains an entire set of the main epiphyseal neuropeptides - substance P, vasointestinal peptide, neuropeptide Y, vasopressin, and several others. Experimental study of epithalamin shows the presence of properties which can be interpreted as nootropic ones. Thus, the drug facilitates the development of conditioned skills in animals, increases the speed of their retraining and intensifies cognitive activity. Moreover, similar to traditional nootropics, epithalamin can activate superoxide dismutase and limit LPO reactions.

The analysis of our own and published data certainly pointed at an obvious similarity between the pharmacological activity of epiphyseal neuropeptides and the effects of melatonin. On this basis, we suggested that the action of epithalamin is achieved through activation of the secretory activity of the gland, i.e. through melatonin. In fact, most epiphyseal neuropeptides in one way or another interfere with the synthesis of the hormone, more often by stimulating it, and a repeated administration of epithalamin increases the plasma level of melatonin. A certain role of the latter is also confirmed by an almost identical set of chrono- and psychotropic properties of both drugs. As long as there is every reason to consider melatonin as a natural nootropic, this provision can be rightfully and completely extrapolated to the clinical possibilities of epiphyseal peptides in the composition of epithalamin.

Some natural monopeptide compounds based on hormones or being hormones themselves, can also act as regulatory neuropeptides with nootropic properties. These include, in particular, Semax which is an analogue of ACTH4-10, and thyroliberin, which have already been described in detail. The only thing to note here is that the high efficacy of semax, proven in clinics, is combined with minimal adverse reactions and the possibility of non-injection administration (through the nose).

In addition to natural neuropeptides, a number of artificially produced compounds of peptide nature claim to be nootropic agents. The search for ligands for the neuronal receptor which piracetam binds with, led to a conclusion that this could be the amide of L-pyroglutamyl-glycine. The thing is that pyroglutamate as an N-terminal amino acid is included in the composition of some peptide hormones (thyroliberin, luliberin). On this basis, several peptide analogs of piracetam - acylprolil dipeptides - were synthesized; of them the most promising one appeared to be N-phenyl-L-prolyl-glycerine ethyl ester called Noopept. Its metabolite cycloprolyl-glycine is found in brain tissue as a natural compound.

As it was shown in a comprehensive study of behavioral, electrophysiological, and biochemical properties of noopept, there is every reason to consider it as a promising nootropic agent. In particular, various experimental models have convincingly demonstrated high anti-amnesic activity, improved transcallosal information transfer, and normalizing effect on pathological shifts caused by ischemia and brain injury or aging. The cellular mechanism of noopept's nootropic effect, which by the way is several times superior to that of piracetam, is determined by complex changes in neuronal function in the form of enhancing cholinergic transmission, limiting free radical processes and glutamate-calcium cascade, and protecting against various types of neurotoxicity.

In order to influence cognitive processes, peptidergic transmission in the brain can be

activated not only directly by means of natural or artificial neuropeptides, but also secondarily, by inhibiting the enzymes that degrade them. This refers primarily to prolyl endopeptidases which under normal conditions participate in the metabolic transformations of many prolyl containing peptides with nootropic properties (thyrolyberine, arginine-vasopressin, substance P). Therefore, compounds of peptide nature with high inhibitory activity towards the above enzymes are available. Their positive effect on cognitive activity, established in different types of amnesia, directly correlates with the degree of inhibition of the activity of prolyl endopeptidases.

34. Question: Can we use the immunological path to treat cognitive disturbances, including with the use of nootropics?

Answer: Since the immune mechanisms are involved in the organization of normal mental activity and their hyperactivity serves as a pathogenetic link in many organic diseases of the brain, this approach looks quite realistic. Indeed, modern researchers reasonably raise a question about the feasibility of including immunotropic agents in the practice of complex therapy of neurodegenerative diseases such as Alzheimer's disease or remote consequences of traumatic brain injury.

However, for a number of reasons, the problem is not solved so easily, primarily because of the rather complex functional relationships within the immune system. Quite a natural desire of researchers to selectively interfere with an individual, strictly determined process sometimes entails a whole cascade of undesirable shifts. For example, the long-approved treatment of neurodegenerative and infectious pathologies with interleukin-2 (aldesleukin) encounters a series of hematological and neuropsychic complications. The latter include memory, vision, and speech disorders which are still difficult to explain. Since the immune system has mechanisms that change the same process in different directions (say, Th-1 and Th-2 lymphocytes, pro- and anti-inflammatory cytokines, etc.), it clearly makes no sense to carry out unambiguous immunosuppressive or immunostimulatory global interventions.

In this regard, the most promising approach is obviously the immunomodulatory one which allows the immune system itself to make adjustments to its own activity taking into account the emerging circumstances. The therapeutic potential of immunomodulators, grouped under the name of cytomedins which are polypeptide extracts from various animal tissues, is most likely based on a similar principle.

The most well-known cytomedins include thymalin (the active principles of the thymus), epithalamin (peptides of the epiphysis), and cortexin (a complex of compounds from the gray matter of the endbrain). After their systemic administration, the learning ability improved in experiment and in children with mental retardation, attention and verbal memory increased in patients with Alzheimer's disease, multiple sclerosis or traumatic brain injury. They proved well in the elderly, increasing their mental and physical performance. Such an optimization of mental activity coincided with the normalization of electrical activity of the brain, immunological indicators, and somatic status in people.

Since intrinsic immunotropic agents have such a clear therapeutic potential in cognitive disorders, then the presence of an immunological component can be expected a priori in nootropics themselves. Although currently this question cannot be considered truly elaborated, the available evidence makes its formulation quite relevant. In particular, it has been shown that nootropics interfere both with the system of 'immune surveillance' in the brain itself and they also modulate the state of the immune mechanisms in the periphery.

For example, in-vivo and in-vitro brain cell culture experiments with cerebrolysin revealed a protective effect on microglial elements, which prevented their activation by various antigens, including lipopolysaccharide, and the subsequent production of proinflammatory cytokines. On the contrary, the production of nerve growth factors was markedly increased. In rat brain homogenates, the vasodilator nicergoline showed a normalizing effect on the neutrophil function with the restriction of free-radical processes.

Nootropic agents can also mediate the functioning of the peripheral organs of the immune system. Piracetam can normalize the thymus function; and at the same time, it attenuated memory disturbances in thymectomized animals. Systemic administration of this nootropic decreased the number of antibody-producing splenocytes in the spleen by inhibiting the differentiation of B-lymphocytes. On the other hand, acting as an immunomodulator, it increased the number of leukocytes and small lymphocytes in rat blood plasma and restored phagocytic activity in severe somatic patients. Addition of piracetam to human polymorphonuclear cell culture increased their metabolic activity.

Lastly, if we classify the epiphyseal hormone melatonin as a typical nootropic, its clinical benefits cannot be ignored as well. As a strong antioxidant and immunomodulator at the same time, melatonin provides elimination of cognitive disorders caused by brain ischemia, neuro intoxication in animals, and age-related mnestic disorders in humans. For therapeutic purposes, the hormone can be primarily indicated for restoration of cognitive functions in cases of desynchronosis arising from a breakdown of circadian periodism.

Thus, there is reason to believe that the immunotropic activity makes a certain contribution to the spectrum of the therapeutic action of nootropic drugs.

35. Question: Is the inhibition of apoptosis part of the specific activity of nootropics?

Answer: One can a priori hardly doubt this if we keep in mind that apoptosis is triggered and maintained by the same processes that serve as a target for the action of nootropics. Indeed, the spectrum of polyvalent action of these drugs includes the fight against consequences of oxidative stress, hyperactivation of excitatory mediator amino acids, mobilization of nerve growth factors, etc. That is why modern researchers reasonably bring up the question of the necessity to counteract apoptosis by searching for its effective regulators and of including this approach in the complex therapy of ischemic and neurodegenerative brain lesions.

The accumulated evidence confirms the feasibility of such a stand. Thus, the endogenous compound citicoline which possesses pronounced nootropic properties, in

parallel with decreasing the number of apoptotic neurons in the dentate gyrus of the rat hippocampus, also enhanced the synthesis of phospholipids and acetylcholine in the brain, weakening the neurotoxic activity of the beta-amyloid peptide. And all this correlated well with its anti-amnestic effect in the model of the passive avoidance reflex.

Similarly, cerebrolysin demonstrates extensive antiapoptotic properties and it can intervene in a variety of stages of the neuro destructive process. Along with the antioxidant effect, it provides neuroprotection in the model of kainate cytotoxicity, increases the level of synaptophysin as a specific marker of the function of presynaptic endings, reduces the activation of microglial elements, and lastly, acts as a typical neurotrophic factor. As a result, according to some researchers, the therapeutic advantages of cerebrolysin are almost entirely determined by the correction of neuroapoptosis in the brain tissues subject to destruction.

Some pyrrolidone derivatives are also aimed directly at limiting apoptosis. Nefiracetam successfully inhibited the death of isolated cortical neurons of mouse embryos by increasing their survival under unfavorable conditions. The neuronal death was determined by apoptosis because it was accompanied by condensation and fragmentation of the cell nuclear apparatus. Interestingly, the anti-apoptotic effect of the nootropic was not reproduced after adding calcium channel blockers (nifedipine or verapamil) to the medium. The anti-amnestic properties of nefiracetam are largely attributed to the restriction of apoptosis.

Aniracetam, nefiracetam, and vinpocetine protected rat astrocytes in tissue culture from ischemic damage that stimulated apoptosis. Their introduction into the incubation medium sharply reduced the number of apoptotic cells, which coincided with the stimulation of mitochondrial functions, and accumulation of intracellular high-energy compounds. The given data are presented in the papers of Gabryel et al. (2002), who also managed to discover a phenomenon which is extremely important, in our opinion. As it turned out, the severity of the neuroprotective effect of conventional nootropics depends on the inhibition of the activity of caspases, in particular, caspase-3, that control the final stage of apoptosis.

Consequently, pharmacological regulation of apoptosis shall play a significant role in the origin of cognitive enhancement, which is largely determined by neuroprotective properties of nootropics. And one of the potentially promising ways to regulate its expression is likely to be the inhibition of the enzymatic activity of caspases.

36. Question: What is the essence of the whole range of inner mechanisms of the action of nootropics?

Answer: Judging by the previous answers, at the cellular and molecular level the nootropic action in the form of an improvement of cognitive processes is realized in many different ways. In generalized form, all of them, in our opinion, can be summed up into three main groups: 1. provision of protection of nerve cells (neuroprotection), 2. regulation of synaptic control of their activity and 3. change of cerebral hemodynamics and rheological properties of blood. Each of these groups, in turn, includes several different mechanisms, and the ways of neuroprotection are the most diverse of them.

1. Provision of protection of nerve cells

Neuroprotection with nootropics in conditions of cerebral pathology can be achieved by: a) increasing regenerative processes in the brain tissue, b) protecting neurons from damaging effects, c) increasing the supply of cells with oxygen and nutrients.

a) Mobilization of neurotrophic growth factors which improve the cell process repair, inhibit apoptosis, and facilitate neurotransmitter function, is very promising in the drug enhancement of regenerative processes. Certain nootropics either act as neurotrophins themselves or stimulate their formation. Another way of regeneration is to ensure neurogenesis, including through enhancing the production and differentiation of stem cells. At the neuronal level, it seems important that nootropics can support the cytoskeleton and microtubule state and provide membranotropic action in the form of increased formation of membrane phospholipids, changes in lipid bilayer viscosity and membrane fluidity.

b) Nootropics also use a variety of mechanisms to protect the nerve cells from damage. One way is to limit the expression of genetically programmed cell death or apoptosis. More common ways are aimed at limiting the damaging effect of various kinds of endogenous neurotoxins, as well as exogenous (pharmaceutical, microbial) toxic agents. The destructive endogenous factors include hyperactivity of free radical processes, which is attenuated by many nootropics with antioxidant properties, able to counteract the oxidative stress. Since nitric oxide and its derivatives often act as aggressive free radicals, limiting their activity is of certain importance in the nootropic action (question 21). Among the endogenous factors, an essential one appears to be the negative role of glutamate excitotoxicity and activation of the glutamate-calcium intracellular cascade. In this regard, the suppression of NMDA receptors, blockade of membrane calcium channels, which ultimately reduce the content of ionized calcium in neurons, can provide reliable neuroprotection. The same goal is achieved by reducing the production of intracellular products such as beta-amyloid peptide or methyl-4-phenylpyridine, which cause severe forms of neurodegenerative pathology (Alzheimer's disease, parkinsonism). Lastly, it is possible to protect the nerve cells from damage by limiting autoimmune and inflammatory reactions due to immunomodulatory and anti-inflammatory activity of the substances.

c) Nootropic agents can increase the energy potential of neurons for their metabolic protection. This occurs due to increased oxidative phosphorylation processes as a result of hypoxia mitigation, activation of the succinate oxidase pathway of energy metabolism, activation of anaerobic glycolysis, and more complete utilization of lactic acid. Since cognitive impairment is often accompanied by a decrease in carbohydrate intake, there may be a value in the activating effect of some nootropics on the synthesis of glucose transport protein which transports glucose across the blood-brain barrier to ischemic brain areas.

2. Regulation of synaptic control of neuronal activity

This is one of the common ways of pharmacological optimization of the functioning of nerve cells, and it is associated with an involvement of various neurotransmitter systems in response to a nootropic influence. Among synaptotropic agents, cholinergic drugs and primarily anticholinesterase agents that universally stimulate the function of both M- and H-cholinergic synapses, stand out for their antiamnesic activity. Excitatory mediator amino acids, in particular glutamate, are also among the common activating transmitters. In

neuronal depression, drug triggering of cholinergic and glutamatergic mechanisms plays a very significant role. Other neurotransmitters - dopamine, serotonin, and noradrenaline - are also involved in the nootropic effect. GABA performs a dual, metabolic and inhibitory, synaptic mission in the brain tissue, ensuring different aspects of pharmacodynamics of GABA-ergic nootropics. It is worth noting that without a specific case it is not always possible to predict a priori which type of drug mediation in synaptic transmission, stimulating or blocking, shall be used to achieve the clinical progress.

3. Changes in cerebral hemodynamics and blood properties

Primary, and more often secondary dilation of cerebral vessels underlies the specific activity of many nootropic drugs. In the ischemic brain, medication-induced vasodilation is an effective way to normalize oxygen and carbohydrate-protein metabolism of nerve cells. Facilitation of patency of small arterial trunks and improvement of rheological properties of blood are also favorable for the recovery of cerebral circulation. Nootropics which disrupt platelet aggregation and increase erythrocyte deformability, help to increase blood fluidity and capillary recanalization.

Thus, modern nootropic drugs have a rich set of ways at the cellular and molecular level to optimize the function of cerebral neurons, which is sometimes severely damaged in organic mental insufficiency of various genesis. Since morpho-functional disorders are based on a variety of mechanisms, it is advisable to apply the complex approach to nootropic treatment as well. Indeed, such a precondition is met by the pharmacodynamics of not only compounds from the list of racetams known for their universal properties, but also representatives of several other pharmacological groups (neuropeptides, vasodilators, synaptotropic drugs, etc.). In most cases, this allows us to ascertain the complex, multifactorial nature (polycomplexity) of the mechanism of their nootropic effect.

CHAPTER IV. PHARMACOLOGY OF NOOTROPICS

37. Question: Classification of modern nootropics, how does it look?

Answer: Despite the relatively long history of study and use of nootropics, their classification that would satisfy both pharmacologists and clinicians, is still lacking. On the one hand, the reason for that is extreme diversity of the group and versatility of the action of its substances; on the other hand, there is uncertainty and vagueness of the concept of the "nootropic effect" itself. That is why researchers are forced to adopt different classification approaches which are not far the best of all.

Thus, one of the first and most comprehensive Russian classifications of nootropics was based on the chemical structure and the mechanism of the cellular action of substances. It included 8 main groups of drugs:

1. Pyrrolidone derivatives: piracetam, etiracetam, oxiracetam and others.

2. Dimethylaminoethanol derivatives: dimethylaminoethanol, meclofenoxate, euclidan and others.

3. Pyridoxine derivatives: pyritinol, gutimin.

4. GABA derivatives: nicotinoyl-GABA, phenibut, pantogam, gammalon, sodium oxybutyrate and others.

5. Cerebrovascular agents: nicergoline, vinpocetine, vincamine, hydergine and others.

6. Neuropeptides and their analogues: ACTH and its fragments, vasopressin and oxytocin, thyroliberin and melanostatin, endogenous opioids, pyroglutamyl, dipeptides.

7. Antioxidants: 2-ethyl-6-methyl-3-oxypyridine, ionol.

8. Various substances with a component of nootropic action: aethimizolum, orotic acid, methyl glucorotate, oxymetacil, xanthinol nicotinate, ginseng, lemongrass and others.

Later, this classification was modified and extended with a focus not on the chemical structure, but on the pharmacological properties of the substances. In the updated form, it consisted of two large groups: nootropics with a dominant mnestic effect ("cognitive enhancers") and agents of mixed type ("neuroprotectors"). Each of them is represented by several subgroups:

I. Nootropic drugs with a dominant mnestic effect.

1. Pyrrolidone nootropics (racetams), mainly of metabolic action: piracetam, oxiracetam, aniracetam, pramiracetam, rolziracetam and others.

2. Cholinergic agents: enhancement of acetylcholine synthesis and release (choline chloride, phosphatidylserine, lecithin, acetyl-L-carnitine, aminopyridine derivatives and others), cholinergic receptor agonists (oxotremorine, bethanechol, spiropyridines, quinucleotides and others), acetylcholinesterase inhibitors: physostigmine, tacrine, amiridine, ergastigmine, galantamine, metrifonate, velnacrine maleate and others, substances with a mixed mechanism: deanol aceglumate, nerve growth factor, sulbutiamine, bifemelane and

others).

3. Neuropeptides and their analogues: ACTH1-10 and its fragments, ebiratile, semax, somatostatin, vasopressin and its analogues, thyroliberin and its analogues, neuropeptide Y, substance P, cholecystokinin-8, peptide analogues of piracetam (GVS-111), prolyl endopeptidase inhibitors.

4. Substances with an effect on the excitatory amino acid system: glutamic acid, memantine, milacemide, glycine, D-cycloserine, nooglutyl.

II. Nootropic drugs of mixed type with a wide range of effects ("neuroprotectors").

5. Brain metabolism activators: acetyl-L-carnitine, phosphatidylserine, homopantothenic acid esters, xanthine derivatives of pentoxifylline, propentofylline, tetrahydroquinones, etc.

6. Cerebral vasodilators: vincamine, vinpocetine, nicergolin, vinconate, vindebumol, etc.

7. Calcium antagonists: nimodipine, cinnarizine, flunarizine, etc.

8. Antioxidants: mexidol, dibunol, exifone, pyritinol, tirilazad mesylate, meclofenoxate, aterovit (alpha-tocopherol and meclofenoxate), etc.

9. Substances with an effect on the GABA system: gammalon, pantogam, picamilon, digam, nicotinamide, phenibut, phenotropil, sodium oxybutyrate, neurobutal, etc.

10. Substances from different groups: aethimizolum, orotic acid, methylglucorate, oxymetacil, beglimin, naftidrofuryl, cerebrokrast, ginseng, lemongrass, etc.

As you can clearly see, this version of the classification is much more comprehensive compared with the previous one and it includes many new substances. As such, while becoming more pharmacologically oriented, it nevertheless turns out to be very cumbersome, partly because of inclusion of a whole range of compounds that are little known and sometimes clinically still insufficiently tested.

In order to simplify the task and bring the classification of nootropics closer to the needs of practical medicine, another version is recommended, which is based on the focus of the pharmacological effect. Our modified version of this classification can include 4 main groups of drugs:

1. Substances with a pronounced psychoenergizing component, which are effective in child mental retardation, in trauma, alcoholism, ischemia: piracetam, pyriditol.

2. Substances with a relatively strong nootropic action for the treatment of amnesia, which are effective in neurodegenerative CNS diseases (senile dementia, Alzheimer's disease): centrophenoxine, pramiracetam, aniracetam, choline and lecithin.

3. Cerebral protectors with a predominant action on the cerebral blood flow, which are used in cerebral circulation disorders: vinpocetine, picamilon, nicergolin, vincamine.

4. Substances with an auxiliary action, directly involved in the metabolism of the nerve cells: orotic and nicotinic acids.

However, this principle of classifying nootropics cannot as well be deemed sufficient. Here we encounter another extreme which is an excessive limitation of the range of nootropic drugs and a not very successful attempt to assign certain clinical indications to strictly determined substances.

Considering the problems outlined above, we suggest our own version of the classification, less simplified than the previous one, but at the same time, in our opinion, not too cumbersome.

1. Pyrrolidone derivatives or racetams: piracetam, oxiracetam, aniracetam, pramiracetam, nefiracetam.

2. Drugs with synaptotropic action:

a) Cholinomimetic agents: anticholinesterase compounds (physostigmine, rivastigmine, tacrine, amiridine, donepezil) and mediator precursors (choline, citicoline, glitimine).

b) GABA-ergic agents: gammalon, pantogam, picamilon, phenibut, sodium oxybutyrate.

c) Glutamatergic drugs: glutamic acid, selective glycine site stimulators - glycine, D-cycloserine, NMDA receptor blockers (dizocilpine, memantine).

d) Dopamine mimetics: levodopa, midantan, selegiline.

3. Neuroprotectors: calcium channel blockers (nimodipine, cinnarizine), antioxidants (mexidol, meclofenoxate), membrane stabilizers (phosphatidylserine, acetyl-L-carnitine, Ginkgo biloba preparations (bilobil)).

4. Cerebral vasodilators: vinpocetine, vincamine, nicergoline, pentoxifylline, xanthinol nicotinate.

5. Neuropeptides, hormones and hormone-like agents: cerebrolysin, neurotrophin synthesis stimulator idebenone, vasopressin and its analogues, dipeptide analogues of piracetam (noopept), ACTH4-10 preparations (semax), thyroliberin and its derivatives (taltrien), and thyroid hormones (thyroxine, triiodothyronine), ovarian hormones (estrogens), epiphysis hormone melatonin.

The proposed classification of nootropic agents is not free from shortcomings as well. In particular, we failed to build it entirely on a functional basis. The chemical range was preserved as a special group of pyrrolidone derivatives (racetams) which have the most pronounced universal properties (stabilization of cell membranes, vasoactive, antioxidant, synaptotropic, and other effects). We deemed it reasonable to single out the group of synaptotropic agents, which turned out to be the largest one, but the clustering of the vasodilators group is not that logical since they have a diverse cellular action. This is more of a tribute to tradition rather than common sense.

We may assume that in the future new nootropic drugs would appear as they are urgently needed by modern clinical practice, and therefore the classification of substances is likely to be modified repeatedly.

At the same time, in the context of nootropics, it seems reasonable to distinguish a group of nootropic-like agents which facilitate cognitive activity along with some main specific effect. These may include many types of psychotropic drugs: herbal adaptogens (ginseng, leuzea, lemongrass, eleutherococcus), psychomotor stimulants (caffeine, sydnocarb), benzodiazepine anxiolytics, representatives of various antidepressants, and stimulants of peripheral, in particular, retinal receptors (like strychnine), antiaggregants, anti-inflammatory drugs, and vitamin complexes.

38. Question: In general what are the pharmacological properties of nootropics?

Answer: They are quite diverse and can be divided into: 1. psychotropic effects and 2. reactions not connected with an influence on mental processes. The first ones have specific and nonspecific nature.

Obviously, the specific one shall be considered the nootropic activity itself. However, researchers put different meanings into this concept. Thanks to Giurgea who proposed the term, it can be interpreted in different ways. Since *noos* means thinking, mind, we are talking here about the possibility of medicinal improvement of the thinking processes in general, and therefore it is not clear which aspects of higher nervous activity are meant and whether the action of substances is directed at sick or healthy people. If we consider that their target is the deterioration of mnestic functions as a result of fatigue in a healthy person as well, then the nootropic effect is essentially indistinguishable from the psychomotor stimulation.

That is why, if we still want to use this term which does not meet the present-day requirements, it needs to be broadened and interpreted more specifically. In our opinion, nootropic activity refers to an ability of psychotropic agents to eliminate cognitive dysfunction arising from various lesions of the brain, or in another interpretation, to eliminate manifestations of organic mental insufficiency. And the basic components of the therapeutic action are an improvement of memory and learning, perception and attention.

The obligatory background only from which this effect can be revealed, is the deterioration of cerebral hemodynamics and tissue hypoxia originating from age, a traumatic brain injury, a stroke, as well as from various forms of exo- and endotoxic damages to central neurons. With such a diversity of causes, there are also many ways of nootropic action of drugs at the molecular and cellular level, already described not only in the series of answers given here (see chapter III), but also in the aggregate. The variety of ways to optimize the pathologically altered nerve cell function also explains, by the way, the complex nature of the classification of nootropic agents, which pharmacologists and clinicians are compelled to use.

Along with a specific effect, these substances also have a nonspecific action on the mental sphere. Side psychotropic activity can quite successfully complement the main nootropic effect and correct mental disorders which accompany organic mental insufficiency. These disorders are found in fatigue, asthenia of patients, onset of neurotic status and the development of depressive states. Meanwhile, nootropics have psychostimulant, anxiolytic and antidepressant properties. Even though they are weaker compared with psychotropic drugs of corresponding pharmacological groups, in the overall picture of the therapeutic effect they are undoubtedly very valuable at times.

One of such properties is psychostimulation. Many types of organic cerebral pathology are accompanied by a decrease in mental and physical performance, decreased general activity and motivation, lack of communication, mental inertness. Repeated use of a number of nootropics largely weakens these phenomena, which allows us to speak not only about psychostimulatory, but also about anti-asthenic action of substances. The reason here is their

stimulating effect on some neurotransmitter mechanisms (monoaminergic, EAA-ergic) with subsequent weakening of the function of cerebral restraining formations like striatum, which makes nootropics closer to psychomotor stimulants like caffeine or fenamin.

Another useful property is an anxiolytic effect which in some representatives of nootropics is expressed quite clearly. Age-related deterioration of cerebral circulation, traumatization, and strokes are often characterized by emotional instability, inadequate reactions to common stimuli, i.e. clearly pronounced signs of neurotic state. This forces patients to resort to the help of traditional anxiolytics. In the meantime, their own anti-anxiety activity accompanies the action of GABA-mimetic nootropics (especially phenibut, picamilon), mexidol, calcium channel blockers, etc. With the help of such properties it is possible to stabilize the emotional status of patients, eliminate increased anxiety and accompanying sleep disorders. The main role is probably played by the inhibitory effect of the substances on the excitability of the emotive limbic structures due to the inclusion of inhibitory GABA-ergic mechanisms.

Apparently restriction of anxiety is a component of two other properties sometimes specifically highlighted in the pharmacology of nootropics - their anti-stressor and adaptogenic action. Due to them, social adaptation of people after disabling brain lesions is facilitated, and tolerance to various loads of exogenous and endogenous nature, having a stressor factor in its core, grows.

The non-specific psychotropic activity of nootropic drugs must also include their effect on depressive and sub-depressive manifestations. They are typical both for cerebral hemodynamic disorders and neurodegenerative diseases (Alzheimer's disease, parkinsonism) and are often characterized by the steady mood depressing. Nootropics turn out to be quite effective in mild and relatively uncomplicated depressive states, and at the same time they potentiate the action of traditional antidepressants and allow to overcome pharmacoresistance. The antidepressant activity is obviously based on the dopamine mimetic properties of the substances and the elimination of the chronobiological disorders typical of depression.

To a certain extent, the chronic pathological phenomenon includes sleep disorders that have a negative effect on cognitive activity and the psycho-emotional status of people. Almost the majority of organic cerebral pathologies are accompanied by insomnia in one form or another. By eliminating such dysrhythmia and normalizing nighttime sleep, nootropics thereby demonstrate hypnotic properties which can also be determined by their psycho stabilizing effect.

In addition to psychotropic activity (specific and nonspecific), nootropics have other pharmacological effects, some of them have a certain therapeutic value. This applies to such side types of central action as anticonvulsant, antiparkinsonian, antidyskinetic. Corrective effect on the immunological status in the brain tissue and in the periphery, the immunomodulatory activity makes a definite contribution to the genesis of the specific psychotropic properties of the substances.

39. Question: Where can we apply the specific psychotropic activity of nootropics?

Answer: These substances are primarily used in psychoneurology to treat cognitive disorders in the form of typical disorders of memory, learning, perception and attention in the organic pathology of the brain. In this regard, nootropics are widely used to combat ischemic and neurodegenerative diseases in geriatric and pediatric practice, in acute and chronic disorders of cerebral circulation, traumatic brain injuries, neuro intoxication of different origin (of infectious and alcoholic genesis, in case of chronic poisoning with drugs and other toxins).

One of traditional areas of application of nootropic drugs is the therapy of amnesic manifestations in old age, which are concomitant with physiological aging and various forms of dementia (senile, vascular, associated with neurodegenerative pathology such as Alzheimer's disease or Parkinsonism). The mnestic defect varies in severity and dynamics depending on the type of lesion, but at all events is associated with the atrophic process in the cortex and subcortical structures and requires medicinal correction with nootropics which have a various mechanism of the cellular action. Upon that, the emphasis is made on overcoming the deficiency of neurotransmitters, primarily acetylcholine, increasing regenerative processes and protecting neurons from damage, as well as improving cerebral hemodynamics.

Under treatment, patients become less exhausted, more focused, their attention becomes more sustained, memory of current events improves, abstract thinking is optimized, their mood, general and social activity get better. Concurrently certain neurological (headaches, dizziness) and mental (anxiety, insomnia, etc.) symptoms weaken.

In general, the effectiveness of the therapy depends on the depth of organic defect, the nature of the medicinal action, and the individual pharmacological sensitivity of the patient. It is quite understandable that mild and moderate conditions respond to the treatment better, but as a rule it tends to be of low effectiveness in case of far aggravated pathology and large-scale nerve cell degeneration.

Given the role of cholinergic deficiency in the pathogenesis of dementia, substances that enhance cholinergic transmission, such as anticholinesterase compounds (rivastigmine, tacrine, donepezil) and acetylcholine precursors (choline, citicoline) are used as anti amnestic agents more often. However, we must recognize that not all patients respond positively to cholinomimetics. Besides, they pretty much only help to delay further progression of the neurodegeneration resuming with the same intensity soon after the therapy is discontinued. In some cases, it turns out more effective when the MAO-B inhibitor selegiline (especially in parkinsonian dementia) or the glutamatergic transmission modulator memantine is additionally prescribed.

A serious alternative to synapto-tropic enhancers of cognitive activity can be the anti-amnesic effect of drugs that improve neuronal regeneration, in particular, the use of cerebrolysin with its neurotrophic properties. In contrast to anticholinesterase agents, the

anti-dementia effect of cerebrolysin shows faster, already after a short course of treatment, and is maintained for a long time (for several months). The combination of the peptide drug with donepezil or amiridine allows to obtain even more pronounced therapeutic changes with fewer adverse reactions. It is also essential that cerebrolysin can be used to prevent early stages of vascular dementia in patients with dyscirculatory hypertensive or atherosclerotic encephalopathy.

The positive effect of extracts from the Ginkgo biloba plant in such preparations as Ginkocer or Bilobil has also been shown in patients with early signs of cognitive insufficiency. In severe dementia they are of little efficacy along with vasodilators such as nicergoline. At the same time, epidemiological studies show a reduced risk of dementia of the Alzheimer's type in women who have received long-term replacement therapy with estrogens. Since they as such can provoke oncological diseases, a selective modulator of estrogen receptors raloxifene which is devoid of this kind of side effects, has been proposed.

Meanwhile, racetams including piracetam, are markedly inferior to the drugs described above in terms of anti-dementia activity and clinicians offer very contradictory opinions about their reliability. In this regard, some authors who apparently identify the nootropic effect with the action of racetams alone, draw a conclusion that nootropics in general are of low effectiveness in dementia.

Nootropic agents are constantly used not only in geriatric practice, but also in pediatrics. The objects are children with consequences of intrauterine hypoxia, birth injury, with mental retardation, including such severe lesions as Down's syndrome and oligophrenia. In case of birth injury doctors resort to parenteral administration of piracetam and similar substances in the first hours after birth, and in later periods - to cerebral vasodilators. These agents, as well as cerebrolysin, are used in neuropediatrics in case of attention deficit and motor hyperactivity which are regarded as a version of minimal cerebral dysfunction which manifests itself in the form of chronic behavioral disorders.

After several courses of treatment with nootropics, defects of attention concentration are alleviated, children become less distracted, impulsiveness is less pronounced, and excessive motor activity also gets restricted. Due to an improvement of memory, substances help to better overcome difficulties that arise in the process of learning, its indicators get enhanced. Children who once fell behind in their academic performance can catch up with their peers. Yet, in severe forms of pathology the effectiveness of the therapy is extremely low.

Acute cerebral circulatory disorders require polyvalent pharmacotherapy, including the use of different groups of nootropics. Their use is aimed at preventing further contagion of the ischemic process at the molecular and cellular level and at correcting long-term consequences of the cerebral excess. In ischemic hypoxia, all drug interventions, including nootropic ones, shall be started as early as possible and carried out in a certain sequence.

Primary neuroprotection is aimed at protection of the brain tissue from oxidative stress and at suppression of the glutamate-calcium cascade; it begins from the very first minutes of stroke and is carried out in the course of 2-3 subsequent days in the form of administration of massive doses of piracetam (intravenous infusion up to 12.0 per day) and mexidol antioxidant

(400 mg). Sublingual administration of high doses of glycine (up to 1.0) is also strongly recommended.

Secondary neuroprotection is resorted to after 3-6 hours from the onset of stroke and it continues for at least 7-10 days, considering it an important measure for the protection of neurons in the zone of ischemic "penumbra". During this period, antioxidants (mexidol) and neuropeptides are specifically recommended: significant doses of cerebrolysin (20-50 ml per day), intranasal application of Semax. If the time is wasted, progressive delayed death of nerve cells rapidly develops in the area of "penumbra", which occurs through the mechanism of apoptosis and eventually leads to an increase of the focus of irreversible damage to the brain tissue.

These measures are believed to timely suspend the pathologic process often making it possible to save the patient's life, and when the acute phase of stroke is finished (on the 20th day) they help facilitate the recovery of motor and cognitive functions. In particular, patients show an increase in spontaneous activity, auditory (especially delayed) memory, tactile and visual spatial recognition.

Unfortunately, not all researchers recognize these clinical capabilities of nootropic drugs. Based on the analysis of numerous results of modern double-blind controlled randomized studies, M. Fischer (2003) comes to a disappointing conclusion that optimistic assessments of the role of nootropics in the fight against acute cerebral circulatory disorders are disputable. In his opinion, other than experimental data, today there is no convincing clinical evidence in favor of the reliability of this method, although there is no need to dispute the advantages of the substances in the reparative period.

Therefore, preventive protection of the brain tissue in patients with high risk of ischemic stroke is now increasingly gaining attention. As shown in experimental models of acute focal ischemia, the preliminary use of various nootropics, in particular, those with vasodilatory properties, is much more effective than after the development of an ischemic damage (Khadzhiev D., 2003).

At the same time, researchers are more unanimous in assessing the clinical capabilities of nootropics in the correction of consequences of traumatic brain injury. Of course, this pathology cannot be regarded simplistically, since of great importance are the degree of the brain traumatization, the location of the area of injury, and the time after traumatization (Gannushkina I.V., 1996; Myakotnykh V.S. et al., 2002). However, in general, the nootropic therapy accelerates rehabilitation of patients, normalizing their psychosomatic status and restoring impaired cognitive functions.

Another area of application of the specific psychotropic properties of nootropics is the treatment of different types of neuro intoxication. These include chronic alcohol poisoning which is viewed as an experimental model of Alzheimer's disease, as well as psychoneurological disorders in psychiatric clinics caused by prolonged use of psychotropic, primarily neuroleptic agents, regular abuse of narcotic agents, and neuroinfections. All these lesions can be classified as neurotoxic effects associated not so much with functional as with morphological damage to nerve cells of the cerebral cortex and subcortical structures involved in the organization of cognitive activity. And all of them are included in the range of

necessary clinical indications for the prescription of nootropic drugs.

40. Question: When can non-specific psychotropic and non-psychotropic properties of nootropics be of demand in the clinical setting?

Answer: In addition to their primary specific action on cognitive functions, the substances have a number of psychotropic secondary effects (antidepressant, anti-anxiety, psychostimulant) that make them popular among psychiatrists. There is a clear range of clinical indications when such properties can be of use with more or less success.

First of all, this refers to the so-called psychoorganic syndromes in the form of a combination of the endogenous psychopathological process with exogenous overlaps caused by traumatic brain injury, neuroinfection, and vascular lesions. For quite obvious reasons, remarkably high efficacy of nootropics is shown in psychiatric patients with cerebral circulatory disorders. In this case, the preparations very successfully complement the often weak specific pharmacotherapy with neuroleptics, anxiolytics or antidepressants. The effect is achieved easier in case of relatively simple structure of the syndrome and a shorter prescription of the disease.

The ability of many nootropic agents to exert antihypoxic and anti-ischemic effects apparently explains their popularity in geriatric psychiatry. The age factor often adversely affects the sensitivity of the elderly patients to traditional psychotropic substances. The combined use with nootropics improves tolerance to these drugs and allows for the use of lower dosages.

With nootropics, positive dynamics in the course of some psychotic disorders is reported, although these substances themselves do not have antipsychotic activity proper and they do not have a direct effect on the positive symptoms of the underlying endogenous disorder. In this situation, an improvement of the nerve cell metabolism and neuroprotection induced by nootropic agents are probably of therapeutic value. It is also essential that they make it possible to overcome resistance to neuroleptics and act as correctors of drug-induced parkinsonism and hyperkineses.

Many researchers note a favorable effect of nootropics on patients suffering from various forms of mental depression, and their particular effectiveness in disorders of cyclothymic nature of medium severity. Patients with pronounced intellectual-mnestic disorders also respond well to the therapy. There is good reason to note the reliability of nootropic GABA-mimetics and vasodilators (vinpocetine, nicergoline) as well. Individual characteristics of the drugs are markedly shown in the speed of delivering clinical benefits. After phenibut, for example, a significant improvement in the condition of patients occurs already on the 2-3 days of treatment, while for piracetam such an improvement is not observed until after 2 weeks of therapy. Mitigation of lethargy and stiffness of the thinking processes and reduction of asthenic manifestations are also described in people suffering from epilepsy. Antidepressant properties of nootropic drugs can be attributed to the dopaminomimetic component in their action as well as the ability to eliminate chronobiological disorders. Nonetheless, in severe depressive-paranoid and

anxiety-depressive syndromes the use of these substances is unpromising.

The existence of anti-anxiety properties in nootropics makes it possible to successfully prescribe them in neurotic and psychopathic states, in case of anxiety before surgery, etc. They reduce the feeling of inner anxiety, improve social adaptation, and normalize night sleep. The ability to stimulate GABA receptors, especially well shown in phenibut, even brings the latter closer in pharmacodynamics to benzodiazepine anxiolytics. In psychiatry, nootropics proved useful in the complex pharmacotherapy of neurotic disorders. Thus, a combination of piracetam with gidazepam made the elimination of mnestic disorders in persons with neurotic status more successful compared to treatment with the anxiolytic alone.

Nootropic drugs have become quite widespread in pediatric psychiatry. They are used in various psychiatric abnormalities in children and adolescents, which arise on the basis of organic and cerebral pathology caused by prenatal and postnatal damages of traumatic, toxic, and hypoxic origin. It is believed that the preparations significantly expand the possibilities of pediatric psychopharmacotherapy. Additionally, they can induce a feeling of vigor and an objectively detected increase in mental performance with improved memory and ability to memorize; these factors increase the educational level of children. This is one of the reasons for their easier adaptation in the group, which, of course, benefits the guided medical and pedagogic rehabilitation as well.

Psychotropic properties of nootropic drugs may also be in demand for the treatment of alcoholism, relief of withdrawal manifestations, treatment of alcoholic psychosis and restriction of addiction. Certain drugs occasionally contribute to the neutralization of toxic products of ethyl alcohol oxidation, and reduction of pathological craving for alcohol. Relieving the symptoms of withdrawal syndrome (anxiety, irritability, depression), they simultaneously prevent the development of alcohol delirium and psychosis.

Thus, the psychotropic side actions of nootropics, although they are weaker than those of the representatives of the corresponding pharmacological groups (neuroleptics, anxiolytics, antidepressants), have proved useful in solving a number of problems of modern psychiatry. At that, their role more often boils down to the potentiation or correction of one or another psychopharmacological effect.

Along with psychotropic action which have proven to be of value in the treatment not only of organic mental insufficiency, but also in the complex therapy of some types of psychopathology, the nootropic agents are also effective in a number of other, mainly neurological diseases. These include convulsive conditions, motor disorders of central origin, headaches, and vestibular disorders. In all cases, the therapeutic potential of the substances obviously depends on the ability to normalize hemodynamics and metabolic processes in the brain.

Some nootropics from GABA-mimetic agents have distinct anticonvulsant properties, therefore, sodium oxybutyrate, for example, is used for urgent relief of seizures of different genesis, and pantogam appears to be a good corrector of the action of traditional anticonvulsants in both grand and minor epileptic seizures.

Patients with hereditary forms of extrapyramidal pathology (cerebellar hyperkineses, hepato-cerebral dystrophy, etc.) showed positive results on the use of pantogam; piracetam

though was less reliable. However, against the background of an improvement in the general condition it too could activate mobility, increasing the speed of motor acts. Continuous prescription of some racetams and pantogam allows to weaken manifestations of chronic extrapyramidal syndrome provoked by neuroleptics. With that, the transformation of the generalized forms of hyperkineses into local ones was noted.

Certain nootropics (pyriditol, picamilon) are quite effective in patients with migraine. Prolonged (30-50 days) use of the substances resulted in a decrease in the frequency and intensity of migraine attacks, mitigation or complete elimination of concomitant symptoms. The results are better in simple forms of the disease with not very frequent episodes. Along with the relief of the clinical condition of patients, normalization of cerebral hemodynamics is also shown. Some substances (vinpocetine, pantogam) were also described as capable of alleviating ordinary headaches as well.

Nooglutil and vinpocetine in experiments and clinics have also demonstrated antinauseant properties. This permits their use for the therapy and prevention of vestibular disorders, labyrinthine vertigo, hearing loss of toxic (medicinal) and vascular origin.

Nootropics have also found application in ophthalmology. Under the influence of cerebrolysin and vinpocetine, an increase in visual acuity was observed due to a decrease in the threshold of light sensitivity of the retina as a result of improved retinal hemodynamics. Due to such properties, the substances are recommended for the treatment of partial optic nerve atrophy, atherosclerotic and angiospastic changes in the retina and even in case of secondary glaucoma.

The above data points to an existence of a fairly wide range of indications beyond the specific psychotropic activity of nootropics. Given the variety of ways of optimizing effects on pathological processes in the brain, there can be no doubt that the range of clinical capabilities of the drugs from this group is far from being limited by the neuropsychiatric disorders listed here and before.

41. Question: How do adverse reactions manifest themselves in the treatment with nootropic drugs?

Answer: Like most medications, nootropics are not without disadvantages which manifest themselves as various adverse reactions, the range of which, though, is quite limited. They can be of a specific nature, which is determined by the peculiarities of the mechanism of action of the substances, but they can also have a nonspecific pattern.

The specific ones include those of the central nervous system and vegetative status. In the first case, the reactions are expressed as multidirectional changes in mental activity. Its undesirable increment is evidenced by such signs as anxiety, irritability, disturbance of night sleep. Unmotivated fears are less frequent. Such complications are provoked by piracetam and some other pyrrolidone derivatives, some GABA-mimetics (aminalon, picamilon), and glutamic acid. Opposite side effects can also develop, they include drowsiness and depressive states which are more often observed during the treatment with cinnarizine or phenibut. As a matter of fact, given the distinct anxiolytic and a certain myorelaxant activity of the latter, it

is not recommended to be prescribed to people whose occupation requires intense attention and motor coordination (transport drivers, surgeons, etc.).

Unfavorable vegetative shifts are most often caused by stimulants of not only central but also of peripheral cholinergic synapses, primarily anticholinesterase compounds. Bradycardia, salivation, increased gastrointestinal peristalsis, abdominal pain and diarrhea which are typical for physostigmine or galantamine, are also common, although to a lesser extent, for anticholinesterases of the new generation - tacrine and rivastigmine. In addition, vomiting, sometimes intolerable, occurs in almost 30% of patients treated with tacrine. Nicergoline, having an alpha-adrenoblocking component in its action, can provoke orthostatic collapse; unwanted hypotension sometimes accompanies the effect of calcium channel blockers (nimodipine). In most cases, the described adverse reactions are characterized by mild intensity and they often regress throughout the course of treatment.

Nonspecific complications do not differ a lot from those that accompany virtually any drug therapy. These include dizziness and headache when using some racetams (piracetam) or picamilon. On the part of the gastrointestinal tract, nausea, vomiting, diarrhea are noted, which are caused by aminalon, piracetam, cinnarizine, picamilon. Allergic phenomena in the form of skin rashes, itching, eczematous skin lesions (pantogam, piracetam, nimodipine) are rather non-specific and relatively infrequent.

Finally, there are complications which are rarely reported only in certain drugs. The action of nicergoline can be accompanied, for example, by unpleasant sensations in the heart area, and piracetam can increase the frequency of angina attacks, mainly in elderly patients. Serious and, fortunately, rare severe complications include hepatotoxic effects inherent in tacrine, and blood damage in the form of anemia and leukopenia in the treatment with glutamic acid.

To sum up the answer to the given question, we must once again emphasize that, despite the need for long-term use, nootropic drugs are characterized by comparative safety and are relatively short of adverse reactions. In addition, there are substances such as cerebrolysin, semax or glycine, which do not cause adverse side effects at all.

CONCLUSION

In modern society, there is a marked increase in the frequency of brain pathology manifested in cognitive impairment. Deterioration of memory, perception and attention are common companions of the aging brain, they accompany intrauterine hypoxia, stroke, traumatic brain injury, chemical and infectious neuro intoxication. A progressive increase in the proportion of the elderly people in the developed countries, the growth of stressful and environmentally unfavorable factors are common causes of mnestic disorders. And the fight against them today in some regions of the world goes beyond a purely medical task, turning into a national social problem.

This state of affairs requires constant research and wide use of drugs that can protect the brain from various exo- and endogenous negative effects, provide a person, regardless of age, the most comfortable life conditions, and accelerate rehabilitation after cerebral excess. Nootropic drugs, which have emerged as an independent group of neuropsychotropic medications over the last 15-20 years, meet these goals.

Further progress of pharmacologists in the field of studying and creating new highly effective substances with such properties largely depends on the achievements of neurophysiology and neurochemistry at the systemic, cellular, and molecular level. It is obvious that successful organization of the cognitive processes at the cellular level needs certain prerequisites. Among the main ones is a full-fledged supply of the brain neurons with blood, and oxygen and nutrients contained in it, primarily glucose. In addition, maintenance of the activity of neuronal associations necessary for the cognitive processes depends on a wide range of neurotransmitter systems of two types. Some of them contribute to an increase in the cell excitability (acetylcholine, excitatory mediator amino acids), others mainly inhibit them (GABA), still others can exercise both types of control (dopamine, serotonin, noradrenaline) through the modulatory effect. Certain hormones and neuropeptides also make a significant contribution to cognitive activity. Among other things, the mnestic properties of hypothalamic thyroliberin, pituitary hormones (ACTH, vasopressin), ovarian estrogens, etc. have been convincingly proven. Melatonin, a hormone of the brain gland of the epiphysis, has attracted considerable attention in recent years, not without reason claiming to be a natural nootropic.

From the neurophysiological point of view, cognitive pathology with its typical deterioration of intelligence, mnestic processes and defects in the sensory sphere is a disintegrative phenomenon. It is based on the deterioration of the activity of individual brain structures and relationships between them. The analytical and synthetic function of the cerebral cortex, its interaction with subcortical formations belonging to the limbic system (such as the hippocampus or amygdala), basal ganglia of the forebrain (striatum), etc. is affected either primarily or secondarily.

Disorders in the sphere of perception are largely determined by the deterioration of the work of analyzers, and the weakening of vision deserves a special place here. Direct (age-related genesis) or indirect (reaction to brain trauma) decrease in the functional state of

the retina, on the one hand, causes restriction of the afferent information inflow to the brain structures, and on the other hand, serves as a source of disturbance of diurnal periodism. Chronobiological defect, dysrhythmic manifestations are common companions of organic mental insufficiency of any origin. Most often this is expressed in night sleep disorders.

From the neurochemical point of view, the weakening of cognitive activity is a consequence of impaired neuronal activity for a variety of reasons. Among them, deterioration of the cerebral blood circulation with inevitable limitation of oxidative and energy metabolism of the brain tissue is undoubtedly in the lead in importance. Progressive chronic limitation of hemodynamics caused by tumor, atherosclerotic lesion of vessels or acute excess (trauma, stroke) necessarily comes down to tissue hypoxia of different severity.

At the same time, increased production of free radicals leads to unfavorable consequences too. Their natural protective function in pathological situations turns into the development of neurotoxic effects. The resulting oxidative stress is the cause of neuronal damage in aging, cerebral ischemia, and neurodegenerative pathology such as Alzheimer's disease. The growing free-radical processes can also coincide with increased formation of nitric oxide. Together they serve as a source of neuronal death through necrosis and apoptosis, among other things as a result of destabilization of the membrane structures.

Undoubtedly, endocrine insufficiency must be recognized as a significant factor that limits the functional activity of neurons in cognitive pathology. Age-related involution of the sex glands accompanied by restricted production of estrogens and testosterone, impaired secretion of thyroid hormones, decreased secretory processes in the epiphysis and decreased production of melatonin - all of these things have an extremely unfavorable effect on the work of neuronal associations, eventually resulting in mnestic disorders.

The understanding of these pathophysiological and pathochemical shifts that determine cognitive disorders, reveals main directions of the pharmacological (nootropic) intervention to alleviate them. However, before a particular drug intervention can be used as a therapeutic agent, it is necessary to obtain reliable experimental evidence of its nootropic activity. And this can only be established with the use of adequate experimental models of cognitive pathology.

At the systemic level, the general meaning of the therapeutic effect of nootropics, aimed at normalizing cognitive activity, shall obviously be narrowed down to the elimination of disintegration in the work of brain structures affected by the pathological process. As far as possible, it is necessary to restore the function of the parts of the neocortex, subcortical centers and their interaction, which are important for cognitive function. The improvement of the work of analyzers, primarily visual perception, and the elimination of chronobiological disorders will also contribute to the alleviation of amnesia and learning problems.

The diversity of pathochemical disorders determines the existence of a wide range of cellular mechanisms on which the therapeutic possibilities of nootropics are based in cognitive pathology. Since the leading role is played by deterioration of cerebral hemodynamics and tissue hypoxia with oxygen and energy deficiency, the ability of nootropics to level hypoxic manifestations seems to be of extreme value. Pharmacological enhancement of protein metabolism is also possible, manifested by activation of protein and

phospholipid synthesis, which are included in the membrane structures of neurons.

Many nootropics have synaptotropic action, increasing the inflow of both excitatory and inhibitory impulses to nerve cells. An enhancement of central cholinergic transmission is essential for their specific pharmacological activity. However, catecholamine-, serotonin-, EAA-, and GABA-ergic synapses can also be involved in the reaction to the substances.

Some hormones and neuropeptides act as nootropics along with artificially created chemical compounds. The anti-amnesic properties of ACTH and estrogen preparations and the nootropic potential of melatonin are of particular interest. The use of synthetic neuropeptides, drugs based on neurotrophins, and immunotropic agents seems to be very promising in the future for the treatment of cognitive disorders.

The wide range of pharmacological effects of nootropic drugs determines an equally wide range of clinical indications for their use. In addition to specific psychotropic activity aimed at attenuation of cognitive disorders of different genesis, in psychiatry they are prescribed as nonspecific psychotropic agents for the treatment of depressive and neurotic conditions. Non-psychotropic properties of nootropics are also applied in neurological practice (therapy of epilepsy, hyperkineses).

Meanwhile, looking back at the last decades of the achievements of the nootropic pharmacotherapy, we regret to state that there has not yet been a rapid breakthrough in the fight against organic mental insufficiency. It is still not possible to cure severe forms of pathology when irreversible neuronal damage has already occurred. In most cases, clinicians are forced to bet not on the recovery of patients, but only on the maintenance of cerebral functions at a level close to normal. The current available pharmacological methods of neuroprotection essentially serve one main task - mobilization of adaptive capabilities of nerve cells and brain structures.

The above considerations allow us to say that reliable nootropics that would meet all the requirements of medicine are yet to be developed. We can only hope this time is not far off.

LIST OF ABBREVIATIONS

ACTH - adrenocorticotrophic hormone
AMPA- 3-hydroxy-methyl-4-isoxazole propionic acid
ATP - adenosine triphosphoric acid
EAA - excitatory transmitter amino acid
EPP - excitatory postsynaptic potential
GABA - gamma-amino-butyric acid
DOPA - dihydroxyphenylalanine
LP - long-term potentiation
CRF - corticotropin-releasing factor
MAO - monoaminooxidase
mRNA - messenger ribonucleic acid
NMDA - N-methyl-D-aspartate acid
NT - neurotrophins or neurotrophic growth factors
PET - positron emission tomography
LPO - lipid peroxidation
cAMP - cyclic adenosine monophosphate
BDNF - brain-derived neurotrophic factor
GDNF – glial-derived neurotrophic factor
NGF – nerve growth factor
NO – nitrogen oxide
NOs – nitrogen oxide synthase
REM – rapid eye movement sleep, paradoxical sleep
TNF – tumor necrosis factor

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(question-answer form)

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