ANTIOXIDANT MEXIDOL. The main neuropsychotropic effects and the mechanism of action.

Author: T.A.Voronina

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Mexidol is an original domestic new-type drug. Its mechanism of action is characterized by antioxidant and cerebroprotective properties.

During the last few years analysts have been paying much attention to studying the role of free radical oxidation in normal and pathological condition and the role of antioxidants in correction and regulation of free radical oxidation in the treatment of various diseases. There are a lot of publications concerning these issues. The scientific foundation of the free radical oxidation theory was laid down by the schools of Russian scientists such as N.N.Semenov, N.M.Emanuel, B.N.Tarusov, U.A.Vladimirov, R.P.Evstigneyeva, E.B.Burlakova, etc. [6-9, 25, 55, 56, 84] and is being developed both in Russia and abroad [62, 63, 66, 68, 69, 72, 75-78, 83].

As is known, free radicals are generated in the organism as a result of metabolism of the oxygen dissolved in tissues. Free radicals are molecules with an unpaired electron on the molecular and outer atom orbit possessing high reactivity. The active oxygen particles are superoxide radical O2, hydrogen peroxide H2O2, hydroxid radical OH which cause the oxidation of membrane lipids, proteins, polysaccharides, nucleic acids. Being strong oxidants free radicals may cause irreversible changes in protein structure and nucleic acids by oxidizing the methionine, histidine, cysteine and tryptophan residues. Oxygen particles initiate a chain reaction of lipid oxidation generating lipid peroxyl and alkoxyl derivatives which are active and take part in dissemination of free radical initiation. These processes flow most actively in the brain which, despite its small

weight, consumes about 20% of oxygen, has unsaturated lipids in its membranes and a low-level antioxidant protection system.

It is assumed that the main process causing the neuron modification is the process of oxidation of unsaturated fatty acids in cellular membrane lipids - peroxidation of lipids which results in the damage of membrane structure-functional condition and its depolarization, the change in the microviscosity of lipidic biolayer and neurons' threshold of sensitivity. The ordered two-layer membrane structure gets distorted and cellular metabolism changes. The membrane organization of lipidic biolayer disorder brings about the change in membrane proteins' conformation, their coordination imbalance which tells upon the ion channels' work, the receptors and ligands affinity, the conjugation of receptor complexes between themselves and with enzyme systems, etc. The oxidation speed of the membrane phospholipids and their content renewal make the basis of the membrane physicochemical system of cellular metabolism regulation which is intertwined with other regulatory systems - that of cyclic nucleoids, phosphoinositide cycle, etc.

Free radicals have good electrophilic properties and can damage cells by necrosis or apoptosis. One of the causes of neuron destruction as a result of lipid repoxidation may become the rise of membrane ion permeability. Specifically, massive calcium introduction activates calcium-dependant proteases and lipases which leads to lysis [28]. Other targets of free radicals' action are DNA of nuclei and cytosolic proteins of the brain neurons, which disturbs the cellular metabolism and can bring about the changes in the genetic code.

The damaging action of free radicals is opposed by the endogenous antioxidant system of the organism which maintains the balance between the free radical oxidation and antioxidant systems eliminating their damaging effects and which includes enzymes (catalase, glutathioneperoxidase, superoxiddismutase, etc.) and endogenous antioxidants (α-tocopherol, vitamin C, etc.). The most famous and well-studied enzyme

is superoxiddismutase which serves as a catalizer for the superoxid anion radical transfer into oxygen and peroxide. There are also hydrophilic (ascorbate, glutathione, etc.) and lipophilic interceptors of free radicals (tocopherols, flavonoids, ubiquinone, etc.).

During the intensive generation if free radicals and inadequate performance of the antioxidant compensatory system there can emerge an oxidant stress that may appear the cause of many pathologies. Free radical oxidation is a main mechanism of the aging of cells, organs and tissues [11, 55, 59, 62, 73, 77, 86] and is involved into the pathogenesis of all the known diseases. Free radicals contribute to many CNS function disorders which accompany diseases and aging: the reduction of vital force, mental and physical efficiency, the psychological and emotional status derangement. Free radical oxidation contributes to the development of such diseases as atherosclerosis [22, 42], cancerous lumps [56, 60, 80], the heart and brain ischemic diseases [24, 58, 74, 81], neurodegenerative diseases: dementia, Alzheimer's sclerosis [24, 61, 64, 82, 90], Parkinson's disease [67, 70, 80], etc. , discirculatory encephalopathy [50], cerebral strokes and hypertension [49,75, 83], stress, neurosis [1, 24, 79], pain syndromes [75], convulsive states [24, 40, 83]. The consequences of free radical oxidation may be also the following: osteoarthrosis, amyloidosis, cholecystitis, pancreatitis, inflammatory processes, the diseases of blood, eye (cataract, etc.), skin, pancreatic diabetes, kidney, liver and lungs diseases, allergic and immunodeficient states, etc.

As the mechanism preventing and eliminating the free radical oxidation-caused damages (endogenous antioxidant system including few antioxidants contained in the cell) can't handle the pathologic process, outward introduction of antioxidant id needed. The search and development of the latter is conducted in two directions. The first is based on the inclusion of endogenous antioxidants such as vitamins E and C into food supplements and vitamin complexes. However, the compensation of natural antioxidant such as vitamin E which having a mild action and which, when introduced into an organism, losses its effectiveness very quickly can not secure therapeutic effect for

serious diseases. That's why vitamins are mostly used as prophylactic and additional drugs in complex therapy.

The second line consists in creating synthetic antioxidants and is undoubtedly a serious achievement of science. Unlike natural ones, synthetic antioxidants exercise more evident and strong antioxidant action. Their mechanism influences the basic components of the pathogenesis of different diseases by restoring the disturbed processes in biomembranes. The first synthetic antioxidant created by N.M.Emanuel for medical application was the phenolic anyioxidant dibunol (ionol). It proved effective for the treatment of urinary bladder cancer, burns and has anxiolytic and anticonvulsant action. There was also registered dibunol's positive effect in the complex CHD therapy. Another phenolic anyioxidant - probucol -is also applied in cardiology. It has a hypolipidemic action protecting lipoproteids with low density from oxidation by increasing their catabolism rate.

Mexidol with its pronounced antioxidant and membrane-protective action takes a special place among such preparations. Its chemical structure looks as follows: 2-ethyl-6-methyl-3-oxyoyridine succinate and resembles that of pyridoxine (vitamin B6). On the other hand, it has succinate as its component which functions in the organism as substrate for increasing the intracellular energy metabolism. Mexidol was synthesize by L.D.Smirnov and K.M.Dumayev [47] in Russian Academy of Sciences, then studied and developed in the Institute of Pharmacology, Russian Academy of Medical Sciences [10-14, 24, 26, 27, 32, 33, 46, 85-90] and National Scientific Center of Bioactive Substances Safety [24, 34, 48].

Mexidol has a wide range of pharmacological effects realized on at least two levels - neuronal and vascular. It exercises anxiolytic, antistress, anyialcohol, anticolvusant, neuroprotective, vegetotropic action [11, 13, 14, 17, 24, 32, 86-90]. Besides, mexidol improves cerebral blood circulation, inhibits thrombocyte aggregation, lowers

cholesterol levels, has cardioprotective and antiatherosclerotic action [18, 19, 22, 23, 41, 54].

Mexidol increases the organism resistance to various extreme factors such as the lack of sleep, conflicts, electric shock, physical exercise, hypoxia, stress, various intoxications including ethanol intoxication. Its important property is the ability to potentiate specific effects of other psychotropic agents, which significantly reduces their effective doses and side effects [10, 24].

Mexidol's main advantage is that it's a low-toxic agent with a wide range of pharmacological properties. It has very few by-effects of traditional neuropsychotropic drugs: exercises no sedative, muscle relaxing, stimulating, euphorizing action and has no side effects of neuroprotective drugs.

In this article the present conceptions of mexidol's mechanism of action are studied and on this basis its main effects (anxiolytic, antialcohol, antiamnestic and antihypoxic) are analyzed.

Mexidol's mechanism of action. Mexidol's fundamental distinction from the most neuropsychotropic agents lies in the absence of its recognition site and specific binding with the known receptors. Mexidol's mechanism of action is determined by its antioxidant and membrane-protective effects with the following key components:

1. Mexidol effectively inhibits free radical oxidation of biomembrane lipids [42, 43, 50, 73], reacts to peroxide radicals of lipids [24, 27, 30], primary and hydroxyl radical of peptides [24, 45].

2. Increases the activity of antioxidant enzymes, specifically that of superoxiddismutase, responsible for the formation and consumption of lipid peroxides and active oxygen forms. [24].

3. Inhibits free radicals during the synthesis of prostaglandin catalyzed cyclooxygenase and lipoxygenase, increases the correlation prostocyclin/ thromboxane A2 and blocks the leukotriene formation [24, 57]

4. Increases the content of polar fraction of lipids (phosphatidyl serine and phosphatidyl inositol) and reduces the cholesterol/phospholipids ratio which proves its lipid-regulatory properties [3-5, 24]; shifts structure transition into the low temperature zones, that is provokes the reduction of membrane viscosity and the increase of its fluidity, increases lipid-protein ration [24, 26, 27].

5. Modulates the activity of membrane-bound enzymes: phosphodiesterase, cyclic nucleotides, adenylate cyclase, aldoreductase, acetylcholinesterase [37, 43, 48].

6. Modulates the receptor complexes of the brain membranes, i.e. benzodiazepine, GABA, acetylcholine receptors by increasing their binding ability [46, 56, 85, 87].

7. Stabilizes biomembranes , i.e. membrane structures of blood cells - erythrocites and thrombocites during their haemolysis or mechanical injury accompanied by the formation of free radicals [24, 37].

Besides, mexidol has a pronounced hypolipidemic action; it reduces the total cholesterol and low-viscosity lipoprotein level in blood and increases the high-viscosity lipoprotein concentration [24]. The preparation improves cellular energy metabolism by activating the energy-synthesizing function of mitochondrion [32, 33]. Changes the monoamine level and increases the dopamine content in the brain [34].

So mexidol's effects are determined by two mechanisms - the antioxidant effect (on both enzymatic and non-enzymatic processes of lipid peroxide oxidation) and the membrane-protecting one, both of which limit the damaging effects of the lipid peroxide oxidation

products, stabilizes the biomembrane of cells, help keep their ordered structure functional organization, particularly the lipid biolayer affecting the membrane-bound receptor complexes, enzymes and ion channels. This may find expression in the allosteric change of receptor confirmation, the establishment of new mechanisms of binding ligands with the most adequate receptor subtypes, the improvement of receptor complexes' conjugation, e.g. through G-proteins or other systems, the change in ion movement, the functioning of the membrane-bound enzymatic systems, etc.

Due to its mechanism of action mexidol exercises a wide range of pharmacological effects and exerts influence on the key components of the pathogenesis of various diseases caused be the oxidation of free radicals. It explains why mexidol has so few by-effects and can potentiate the action of other agents, especially those that realize their action as direct antagonists of receptors.

Anxiolytic action. Mexidol has a pronounced anxiolytic action, can eliminate anxiety, fears, strain, nervousness in different experimental models (a conflict situation, cross-shaped labyrinth, dark-white cameras, etc.). The most detailed analysis of mexidol's action was conducted with the help of Vogel tranquilizer estimation method of conflict situation for rats. The conflict situation was created by suppressing the drinking reflex in rats by the painful electric stimulus when they drank from a drinker-tub. It is based on the confrontation of two motivations - the drinking motivation and the defensive one (the fear of punishment at the attempt of satisfaction of the drinking need) [15, 36]. The tranquilizing effect lies in the elimination of anxiety and fear and the increase of punishable drinkings in the 10-minute period which a rat spends in the cell.

Mexidol has a pronounced anxiolytic activity which is revealed by the significant and statistically reliable increase of the number of punishable drinkings (table 1). The agent exercises its effect when introduced in different doses (25, 50, 100, 200 mg/kg) and different introduction ways (intraperitoneally, intramuscularly, inside). When introduced in the 50 mg/kg dose (intraperitoneally), it has the effect similar to that of diazepam in 2

mg/kg dose and alprazolam in 0.5 mg/kg dose. But unlike benzodiazepine tranqulizers, mexidol retains the reaction adequacy in the conflict situation when Brodi-Naut scale of provoking the test stimuli is used.

Unlike the known tranquilizers, even when used in the highest therapeutic doses (200 mg/kg) mexidol does not have a sedative effect. It does not lower the motion activity of animals in the Opto-varimex unit and does not suppress the orientative-trying reaction in the open field technique. For comparison, the anxiolytic effect of traditional tranquilizers is accompanied by the sedative action. For example, diazepam in the 2 mg/kg dose producing an anxiolytic effect 5 times reduces the motion activity in the open field. Alprazolam (0.5 mg/kg) reduces the motion activity 2.8 times.

Table 1. The anxiolytic effect of mexidol in the conditions of the conflict technique for rats

Substances	Doses mg/kg	Introduction way	The number of punishable drinkings
Control	-	intraperitoneally	19.9±2.1
Mexidol	25	intraperitoneally	29.5±3.5*
Mexidol	50	intraperitoneally	45.5±6.7*
Mexidol	100	intraperitoneally	62.8±5.7*
Mexidol	200	intraperitoneally	76.1±10.8*
Mexidol	200	inside	49.1±7.3*
Diazepam	2	intraperitoneally	44.0±9.2*
Alprazolam	0.5	intraperitoneally	41.9±11.4*
Mexidol+ Bikukullin	100 0.75	intraperitoneally subcutaneously	18.7±8.5**
Mexidol+ Picrotoxin	100 2	intraperitoneally intraperitoneally	15.7±11.3**

Mexidol+ Ro 5-3663	100 10	intraperitoneally subcutaneously	28.1±5.7**
Mexidol+ Ro15-1788	100 15	intraperitoneally intraperitoneally	44.5±11.1**
Mexidol+ CGS-8216	100 3	intraperitoneally intraperitoneally	42.8±7.1**
Mexidol+ Pentilentetrazol	100 25	intraperitoneally subcutaneously	31.3±8.4**
Mexidol+ B-KKЭЭ	100 50	intraperitoneally subcutaneously	82.7±13.5**
Mexidol+ Phenazepam	100 0.1	intraperitoneally intraperitoneally	98.3±7.5**

*Note: * - P < 0.05 in comparison with control: ** - P < 0.05 in comparison with mexidol in 100 mg/kg dose*.

Mexidol does not have muscle relaxant action even in doses that 4-6 times exceed the average therapeutic anxiolytic dose (50 mg/kg) and doesn't have such side effects as movement incoordination in revolving nail test, the reduction of the muscular tonus and mascular force in the test of the reverse reticular platform and the pull-up test. As contrasted to it, diazepam (2 mg/kg) causes the movement incoordination in 60% of animals, alprazolam (2.5 mg/kg) - in 50% of cases.

Thus, mexidol has pronounced anxiolytic action comparable to the action of diazepam and alprazolam in equivalent doses. Mexidol's significant advantage over other tranquilizers lies in the absence of by-effects such as sedative, muscle relaxant and amnestic effects and the retention of adequate reaction in the extreme situation.

Consequently, mexidol can be viewed as a selective "daytime" tranquilizer which exerts its anxiolytic action without extra sedative, muscle relaxant and amnestic effects.

The analyses of mexidol's anxiolytic action is conducted with the help of the analyzers of the GABA-benzodiazepine chlorine-ionophore receptor complex. Tests showed that CGS-8216 and in a lesser degree Ro15-1788 (the antagonists of benzodiazepine receptors), picrotoxin (chloride-ionophore blocker), Ro 5-3663 (blocker of α-dihydropicrotoxin binding and disturbing the conjugation of GABA and benzodiazepine receptors), pentilentetrazol (GABA-antagonist), bikukullin (the antagonist of GABA-A receptor) significantly lowered mexidol's anxiolytic effect. Phnazepam (the agonist of the benzodiazepine receptor) and in a lesser degree β-carbolin-3-carboxyethyl ether (β-ККЭЭ, the inverse agonist of the benzodiazepine receptor) enhanced mexidol's anxiolytic action in the conflict situation (table 1). The findings prove the involvement of the GABA-benzodiazepine chlorine-ionophore receptor complex into the realization of mexidol's anxiolytic action.

On the other hand, mexidol does not bind with benzodiazepine and GABA receptors but it can intensify the binding of the tagged diazepam with benzodiazepine receptors [46, 85, 87].

Thus, not having the direct affinity to benzodiazepine and GABA receptors, mexidol exercises the modifying action by intensifying their binding ability. These data together with the results of the analyses of mexidol's anxiolytic action with the help of analyzers bring the idea that mexidol's anxiolytic mechanism is determined by its modulatory effect on the benzodiazepine chlorine-ionophore receptor complex.

Taking into considerations the modern views on the new type substances that don't refer to the direct receptor agonists, mexidol's mechanism of action may be considered as the effect of a modulator allosterically potentiating the liganda receptor and ion channels activator. We may assume that mexidol brings about the conformational

changes in the benzodiazepine chlorine-ionophore receptor complex and its transition into the conformation of an open channel which forwards the chlorine currents. The mechanism of the anxiolytic effect realization may be also conditioned by the appearance of new varieties of binding endogenous ligands with the most adequate receptor subtypes and by the improvement of the GABA and benzodiazepine receptors' conjugation, which optimizes the functioning of the chloride channel.

Antialcohol action. Mexidol has a pronounced antialcohol action exerting a therapeutic effect on the disorders caused by chronically used ethanol, on the abstinence syndrome and the acute alcohol intoxication.

Within the chronic experiment young eugamic mice (females) beginning with the age of three months have been used 15% ethanol solution instead of drinking water for 5 months. The amount of ethanol used by one mouse in a day was 0.56-0.75 ml (absolute alcohol equivalent). Mexidol was used simultaneously with ethanol in the dose 20-25 mg/day. The examination of the animals' behavior 2 weeks after the 5-month ethanol introduction revealed significant and statistically reliable worsening of learning and memory abilities during the development of active avoidance reflex in the shuttle box. Animals performed a lot of wrong reactions, there were fewer number of correct answers and they were realized with longer latent periods than those in the control group and did not reach the learning criteria even on the 6th day of learning. Mexidol eliminated all the learning and memory disorders in the alcoholized animals (table 2). The mice that were given mexidol were taught reflexes effectively and with the same correct answer factor as the control group.

Table 2. Mexidol's effect on the disturbed learning process after a long period (5 months) of ethanol usage

Groups	The percentage of reflex performance on the different stages of teaching				
	2nd	3rd	4th	5th	6th

Control	4.1±1.3	10.5±1.6	18.8±3.3	31.4±7.3	38.2±.4
Ethanol (5 months)	2.2±0.8*	5.8±1.1*	10.2±2.8*	20.3±5.4*	18.5±5.1*
Ethanol+ Mexidol	9.1±2.3***	24.7±5.3**	31.8±7.7**	41.6±6.5**	56.1±8.1**

*Note: * - P< 0.05 in comparison with control; ** - P< 0.05 in comparison with the ethanol group.*

As is known, the increased amount of lipofuscin in the brain of animals after a long alcoholization period is a result of the lipid peroxidation [65]. To estimate mexidol's antioxidant activity the amount of fluorescent pigment in the cerebral cortex of the alcoholized mice was studied using the corresponding method [71]. The analyses of extracts from the homogenate of the alcoholized animals' cerebrum revealed higher fluorescence intensity than in the control group, which proves the enhanced lipofuscin generation in the cerebral tissues of the alcoholized mice. Mexidol lowered lipofuscin accumulation in the cerebrum, which manifested itself in the fluorescence performance degradation by 2.4 times in comparison with that of the alcoholized animals (table 3). So the restoration of the learning process under the influence of mexidol is accompanied by the lipofuscin amount reduction in the brains of these animals.

Table 3. Mexidol's effect on lipofuscin (according to the performance of the fluorescence of the cerebrum extracts of mice) after a long alcoholization period

Groups	The number of mice	The cerebrum's weight (mg)	Fluorescence/cerebrum
Control	13	465.0±9.8	34.3±1.5
Ethanol	10	470.8±8.3	114.8±7.5*
Ethanol+ Mexidol	11	469.9±11.1	47.5±4.5**

*Note: * - P< 0.05 in comparison with control; ** - P< 0.05 in comparison with the ethanol group.*

Mexidol also affects the neurotoxic presentations of intoxication caused by the single-dose introduction of large ethanol doses (25% solution in 2 g/kg, inside) to animals. The ethanol intoxication reveals in neurological deficit (movement incoordination, muscle tonus reduction, etc.), the disorders of orientative-trying behavior and reflex realization. Mexidol in 100 mg/kg dose (intraperitoneally) eliminates the manifestations of alcohol intoxication: it reduces the disorders of orientative-trying behavior in the open field (table 4), restores the movement coordination in the revolving nail test and the adequacy of their behavior at the burrow reflex realization.

Thus, mexidol has a pronounced antialcohol action. It eliminated the disorders of cognitive functions, of the learning and memory processes caused by a 5-month ethanol introduction ad its cancellation and prevents lipofuscin accommodation in the cerebrum of alcoholized mice. Mexidol fights neurological and neurotoxic manifestations of the acute alcohol intoxication.

Table 4. The elimination of disorders of orientative-trying behavior in the open field caused by ethanol introduction with the help of mexidol

Groups	Doses	Horizontal activity	Vertical activity	Research activity	The number of grooming acts	The number of faecal boluses
Control	-	17.9±2.85	11.5±2.72	7.7±2.21	1.1±0.74	3.4± 1.26
Ethanol	2 g/kg	32.7±8.72*	5.2±3.93*	2.6±1.71*	1±0.82	2.4± 1.35
Ethanol+ Mexidol	2 g/kg +100	15.9±4.84**	2.5±1.96**	4.6±1.59**	2±1.83	2.7± 1.42

	mg/kg					

*Note: * - P< 0.05 in comparison with control; ** - P< 0.05 in comparison with the ethanol group.*

As is known, ethanol cannot bind to specific receptors and exercises its effect due to its presence in the membrane biolayer damaging hydrophobic protein parts or lipid matrix and causing displacements in the lipid phase of biomembranes where membrane-bound proteins are located and membrane damage. The chronic ethanol introduction leads to the activation of lipid peroxidation processes, the reduction of the unsaturated fatty acids to saturated fatty acids ratio which brings about the induration of the membrane structure, the reduction of its fluidity and leads to functional disturbances of receptor complexes, the active and passive ion transport.

We may assume that the mechanism of mexidol's therapeutic effects on alcoholization results is realized on the level of one of the main pathgenetic stages of the ethanol-caused destructive process and is determined by its membrane-stabilizing and antioxidant action, by mexidol's ability to prevent the activation of lipid peroxidation process, to restore the structure-functional state of membranes, their fluidity and phospholipid composition.

Antiamnestic action, memory improvement. Mexidol improves the learning and memory processes and has an evident antiamnestic effect eliminating memory disorders caused by different impacts. Table 5 contains the data about mexidol's (50-200 mg/kg dose, intraperitoneally) ability to eliminate the amnesia of the passive avoidance conditioned reflex in rats caused by maximum electroshock immediately after training and at the reproduction of this skill 24 hours after the ttraining according to the technique described earlier [16]. Mexidol significantly increases the latent period of animal entering into the dark dangerous box and reduces the period of their stay there. Its effectiveness in 50 mg/kg dose equals that of piracetam in 350 mg/kg dose.

Table 5. Mexidol's effect on the amnesia of the passive avoidance conditioned reflex in rats caused by maximum electroshock.

Effect	Doses	The latent period (sec) of the first entering into the dark box ±SEM	The period spent in the dark box ±SEM
Training	-	102.2±14.5	4.7±0.2
Amnesia (maximum electroshock)	-	37.46±9.1*	44.2±7.3*
Mexidol	50	75.14±12.78**	10.7±1.8**
Mexidol	100	91.3±14.8**	19.3±5.1**
Mexidol	200	97.6±15.7**	21.8±5.3**
Piracetam	350	78.0±11.7**	13.20±3.1**

*Note: * - P< 0.05 in comparison with control (trained animals without amnesia); ** - P< 0.05 in comparison with the amnesia caused be maximum electroshock*.

Mexidol exercises its antiamnestic effect on other types of amnesia as well restoring memory disturbed by the introduction of scopolamine or by deprivation of the paradoxical phase of sleep [12, 14, 17, 89]. When the scopolamine amnesia model is used the period that animals spend in the dark box under the influence of mexidol (100 mg/kg) reduces by more than 4 times in comparison to the animals with amnesia which prefer staying in the dark box having forgotten the pain stimulus earlier received there.

Mexidol demonstrates effect both when introduced before the training and the effect of an amnestic factor and when injected immediately after the training and amnestic factor which proves its ability to prevent the amnesia development and eliminate existing amnesia. Mexidol's amnestic action equals and often exceeds in its effectiveness such nootropic drugs as piracetam, piritinol, meklophenoxat, cleregil, pantogam, pikamilon, sodium oxibutirat. Along with the anyiamnestic effect mexidol promotes the preservation of the memory trace and fights the fading of the trained skills and reflexes.

Mexidol exerts the positive recovery action on the disturbed cognitive functions and neurological deficits emerging during the natural aging and in the conditions of the experimental model of Alzheimer's disease [11, 14, 86, 89, 90].

The mechanism of mexidol's positive effect on cognitive functions is conditioned by its membrane-protective and anyioxidant action. According to the synapse-membrane memory organization the main role in the fixation of information in CNS belongs to conformational shifts of protein macromolecules in the synapse zone. The short-term memory is realized through the conformational changes of the nacromolecules of the synapse protein conditioned by the ion shifts caused by the impulse transit through the synaptic contact. When along-term memory is being formed conformational changes not only engage the synapse zone but through the cooperative effect spread on the other neuron membrane complexes creating a single system of interconnected protein macromolecules. As a result protein macromolecules of membrane complexes preserve newly acquired steady conformational states. Thus, the conformation change of the membrane proteins is one of important characteristics of information encoding, preservation and reproduction.

Taking into consideration the lipid-dependence performance of the membrane enzymes and the importance of lipid environment microviscosity for their functioning we can come to the conclusion that mexidol, by exerting influence on the membrane physicochemical characteristics and causing its structure-functional alterations, increases the functional activity of the biomembrane and thus promotes the generation of steady conformational changes of protein macromolecules of synaptic membranes, forwards the generation of interconnected systems of neuron membrane complexes activation the synaptic processes and improving cognitive functions.

It is important to mention mexidol's ability to change phospholipid composition of the outer membrane of the cerebrum synaptosome; for memory functioning the important

factors are the following: the increase of the amount of phosphatidyl serine which affects the activity of potassium and calcic ATPase and phosphotidilizonit which improves the affinity of acetylcholine receptor to acetylcholine.

Antihypoxic action. Mexidol has a pronounced antihypoxic action which manifests itself in the ability of the drug to increase the live interval and the number of survived animals in different hypoxic states: hypobaric hypoxia, hypoxia with hypercapnia in pressure volume and hemic hypoxia. For example, mexidol (100mg/kg dose) increases by two times the life interval of animals with hypobaric hypoxia lifted to the height 11 thousand meter and the number of survived animals - by 2.4 times (table 6). Mexidol's antihypoxic action significantly exceeds that of piritinol and piracetam which in 500 mg/kg dose has low antihypoxic activity in the state of acute hypobaric hypoxia and hypoxia with hypercapnia.

Table 6. Mexidol's antihypoxic action in the conditions of hypobaric hypoxia in mice experiments

Substances	Doses, mg/kg	The period of surviving, min±SEM	Survived animals,%
Control	-	8.9 ±1.8	16.6
Mexidol	100	18.1±4.3*	40.0
Control	-	8.1±1.1	16.6
Mexidol	200	21.3±4.5*	60.0
Control	-	10.1±1.1	22.0
Piracetam	500	1.2±1.2	22.0

*Note: * - P < 0.05 in comparison with control*

The mechanism of mexidol's antihypoxic action is connected with its specific influence on the energy metabolism [32, 33]. Mexidol is an antihypoxant with direct energizing effect: it affects the endogenic respiration of mitochondria activating their function of energy synthesis. Antihypoxic action of mexidol is conditioned not only by its antioxidant

properties but first of all by succinate which in the conditions of hypoxia can oxidize by the respiratory chain while coming into the intracellular zone.

Consequently, mexidol's action is determined by the activation of compensatory metabolic flows delivering energetic substrates (succinate) into the respiratory chain and serving as an emergency adaptive mechanism for hypoxia. Mexidol's antihypoxic action is aimed at the restoration of disorders of the oxidative phosphorylation processes caused by the limitation of NADN-oxidase way of oxidation.

So, mexidol is a new-type neuropsychotropic drug both in the terms of its mechanism (antioxidant, membrane-protector) and in the range of pharmacological effects.

Mexidol is permitted for wide therapeutic application. Clinical studies proved mexidol's high therapeutic effect for the treatment of various neurological, mental and cardiovascular diseases [19, 24]. The preparation revealed high effectiveness in the treatment of neurotic and pseudoneurotic disorders [2, 31, 38, 39, 52], different alcoholism-caused disorders including the abstinence syndrome [20, 29], acute and chronic disorders of cerebral circulation including strokes [18, 41, 51, 49], discircular encephalopathy and vegetovascular histonia [50, 53], the disorders of brain functions caused by aging and atherosclerosis [21, 35, 44], acute neuroleptic intoxication. For clinical use mexidol is delivered in capsules, pills and ampoules (5% solution, 2 ml).

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