in the control group is accompanied by a stable functioning of the glandular tissue. It can play a negative role at a certain stage of ulcerogenesis, hindering the repair process.

Solkoseryl was found to have an effect on ulcer progression: the level of collagen proteins, as well as DNA and RNA, was more stable, which ultimately had an impact on the healing rate of ulcer injury.

A comparative analysis of the ulcerostatic effects of solcoseryl and methyluracil showed a considerable similarity in the mechanism of action of these preparations. However, solcoseryl is likely to inhibit the secretory function of the stomach much more than methyluracil. Earlier we extensively studied the effect of methyluracil on the biochemical indexes of stomach tissue in induced acetate ulcer [2, 3]. Therefore a comparative analysis was not performed. However it should be noted that the dynamics of stomach ulcer progression under the influence of secret and methyluracil exhibited some distinctions, although a certain similarity was also observed. This allows us to assume that only a certain similarity is observed in the mechanisms of the ulcerostatic effect of the preparations mentioned.

Thus, the dynamics of DNA and RNA, collagen, noncollagen proteins, hexoses, and glycosaminoglycans indicates their role in the pathogenesis of induced acetate ulcer of the stomach and allows one to estimate the various components of the mechanism of ulcerostatic action of solcoseryl.

LITERATURE CITED

1. I.K.Asalyuk and P.P.Zhdan, *Vrach. Delo*, No. 3, 24-28 (1980).
2. I.G.Kuznetsov, M.M.Rasulov, L.I.Slutskii, and M.G.Voronkov, *Izv. Akad. Nauk SSSR, Ser. Biol.*, No. 3, 343-352 (1991).
3. M.M.Rasulov, I.G.Kuznetsov, A.A. Belousov, L.I.Slutskii, M.G.Voronkov, *Dokl. Akad. Nauk SSSR*, **313**, No. 2, 501-505 (1990).
4. L.I.Slutskii, Rheumatism (Cells and Colloids, Correlations and Patterns) [in Russian], Riga (1966), pp. 284-297.
5. L.I.Slutskii, Biochemistry of Connective Tissue [in Russian], Leningrad (1969).
6. L.I.Slutskii, *Izv. Akad. Nauk Latv.SSR*, **408**, No. 7, 94-108 (1981).
7. A.Chocha and J.Chmiel, *Diagn. Lab.*, **7**, No. 4, 65-71 (1971).
8. K.Takagi, S.Okabe, and R.Saziki, Japan J. Pharmacol., No. 19, 899-906 (1969).

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Nootropic Drugs Potentiate the Nerve Cell Responses Evoked by Activation of the NMDA-Glutamate Receptors

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The specific effect of nootropics is determined to a great extent by their influence on nerve cell bioenergetics as well as their membrane-stabilizing action conditioned by lipid peroxidation inhibition, accelerated phosphatide circulation and the suppression of free-radical processes [2]. The Neurotransmitter mechanisms of the antiamnestic effect have been less studied [2], but it has been established that blockade of NMDA-glutamate receptors weakens the behavioral effects of nootropic drugs [8,9], while aniracetam increases the excitatory postsynaptic potentials (EPSP) amplitude in pyramidal neurons of the CA1 field, caused by stimulation of the radial layer of rat huppocampus sections [10]. Since EPSP of these neurons can be a result of activation of both N-methyl-D-aspartate (NDMA) and non-NMDA-receptors [6], it is not clear which kind of glutamate receptors is involved in the aniracetam effect described. In experiments on frog oocytes with expressed excitatory amino acids by injection of rat brain mRNA it was found that aniracetam intensifies the transmembrane currents caused by quisqualate and AMRA [7]. Meanwhile, piracetam strengthens the aspartate and glutamate influence on the spinal motoneurons, affecting

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TABLE 1. Effect of Investigated Substances on Amnesia Caused by Maximum Electroconvulsive Shock

Substance investigated	Dose, mg/kg	Number of rats (from 5) reproducing active avoidance habit	
		1 hour later	24 hours later
Piracetam	0	0	1
	200	2	3
	500	3	3
Ethymisole	0	0	0
	10	2	2
	50	3	3
Dimethylaminoethanol	0	0	0
	500	2	3
	1000	3	3
Ambocard	0	0	0
	5	2	3
	10	3	4

the allosteric glycine-regulated parts of the NMDA receptors [3].

In the present work it is shown, that potentiation of nerve cell reactions caused by the NDMA- but not the other glutamate receptors is a common property of nootropics of diverse chemical structure.

MATERIAL AND METHODS

In the model of electroshock amnesia the antiamnestic activity was investigated of piracetam, ethymizole, dimethylaminoethanol (DMAE), and ambocarb. A conditioned reflex of avoidance (CRA) was worked out in rats, combining the effect of a conditioned stimulus (bell, 5 sec) with 2 sec preceding electrical stimulation of the paws (60 V, 7 sec). The animals whose latent time of CRA did not exceed 3 sec were chosen. On the day of experiment CRA presence was checked and solvent or a substance to be studied was injected intraperitoneally. One hour later the acquired conditioned reflex habit was suppressed by maximum electroshock (50 mA, 500 sec) produced through electrodes placed on the ears. CRA reproduction in the control and experimental animals was evaluated 1 and 24 hours after electric shock.

In the experiments on parasagittal sections of the spinal cord in lake frogs with the standard microelectrode technique, as described earlier [1], the influence of the same substances was studied on motoneuron reactions, which were caused by delivering from a micropipette under pressure solutions (10 mM) of L-aspartic (AA) and L-glutamic (GA) acids, or by electrostimulation (0.1 msec, 1 V, 5 sec) of the dorsal root (DR-EPSP). The spinal cord was superfused by a salt solution containing (in mM): NaCl 100, KCl 3, $CaCl_2$ 2, NaH_2PO_4 1.25, $NaHCO_3$ 10, glucose 10; the pH of the solution saturated with a mixture of 95% O_2 + 5% CO_2 was 7.4; flow rate was 1-3 ml/min at 18-20°C. For the suppression of the NDMA-receptor-mediated responses of the motoneurons, ketamine (30 μM) and $MgSO_4$ (2mM) were added to the salt solution. After the attainment of constant values of motoneuron responses for the action of AA and GA or for dorsal root stimulation, the spinal cord was subjected for 5 min to a salt solution containing the investigated nootropic and 5, 10, and 15 min after this was discontinued, depolarization motoneuron responses were

TABLE 2. Effect of Investigated Substances on AA- and GA-Promoted Depolarization Motoneuron Responses and DR-EPSP (M±m)

Substance investigated	Concentration,	Amplitude of motoneuron responses (in % of initial) for superfusion of spinal cord with salt solution			
		containing no Mg(+2)		containing 2 mcM of Mg(+2) and 30 mcM ketamine	
		DR-EPSP	AA	DR-EPSP	GA
Piracetam	100	125,7±6,8*	127,0±3,3*	102,5±2,1*	105,0±4,5
		145,5±7,7*	146,8±5,1*	94,2±2,9	105,2±2,8
Ethymisole	100	129,2±6,9*	139,7±6,5*	101,3±3,8	102,3±2,3
		149,3±8,4*	172,5±6,9*	101,2±6,4	101,1±4,9
Dimethylaminoethanol	1000	148,3±7,9*	151,0±6,7*	97,5±2,8	102,5±2,1
		172,2±3,5*	160,0±5,2*	101,2±9,0	105,0±2,7
Ambocarb	30	135,6±4,7*	142,8±9,8*	103,3±2,5	105,1±2,9
		158,1±5,0*	194,6±12,9*	100,6±4,9	96,2±4,0

Note. The higher and lower values represent responses registered correspondingly at the 10th and 15th minute after the end of the studied effects. Asterisks designate data with $p<0.05$ in comparison to control.

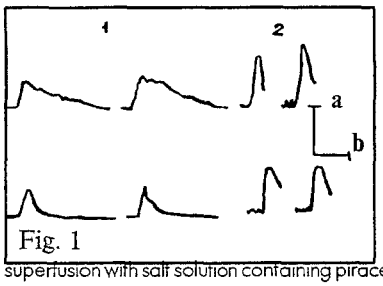

Fig. 1

Fig. 1. Influence of piracetam on DR-EPSP of spinal motoneurons (1) and their depolarization responses (2), caused by L-aspartic (2,a) or L-glutamic (2,b) acids. In each pair of figures, on the left is the initial reaction, and on the right, the reaction 10 min after the end of spinal cord superfusion with salt solution containing piracetam (100 μM) without Mg^{2+} (a) or in the presence of 2 mM magnesium sulfate and 30 μM ketamine (b).

recorded: DR-EPSP or caused by AA and GA. The investigation was conducted on 76 motoneurons, each series on 4-6 cells.

RESULTS

The substances investigated possess an antiamnestic effect, revealed in a dose-dependent increase of the number of animals in which the habit of active avoidance reaction (jumping out on the rod) had been restored after the amnestic action of electroconvulsive shock (Table 1).

It is seen in Fig. 1, that preliminary superfusion of the spinal cord with a solution containing 100 μM of piracetam and free of Mg^{2+} increases the DR-EPSP amplitude at the expense of late components and the AA-caused depolarization responses. The effect of the same piracetam concentration on spinal cord which is superfused with a solution containing 2 mM Mg^{2+} and 30 mg ketamine causes no changes of the amplitudes of GA-promoted depolarization motoneuron responses and DR-EPSP.

Like piracetam, the other substances investigated also increase the amplitude of depolarization motoneuron responses caused by AA and of late DR-EPSP components under spinal cord superfusion with salt solution without magnesium, but under the conditions of ion channel blockade of the NMDA-glutamate receptors by ketamine and Mg^{2+} nootropic drugs have no influence on GA effects and DR-EPSP (Table 2).

It was established earlier that the AA-promoted depolarization motoneuron responses and late DR-EPSP components are mediated by NMDA-glutamate receptor activation, while the earlier ketamine-resistant DR-EPSP components and GA-promoted depolarization responses in the presence of Mg^{2+} and ketamine are connected with activation not of the NMDA-, but of the kainate/quisqualate-glutamate receptors [1]. Thus, the characteristic property of substances possessing antiamnestic activity (see Table 1) is potentiation of the post-synaptic responses of nerve cells, mediated by activation of the NMDA-glutamate receptors (see Table 2).

It is known that the elaboration of conditioned reflexes is accompanied by continuous potentiation of focal synaptic potentials, for example in field CA3 of the hipocampus [10], and in the course of development of continuous potentiation of synaptic transmission, which is the neurophysiological basis of memory and learning, there is a short (up to 20 min) reversible phase, conditioned by NMDA-receptor activation, and irreversible, connected with expression of the kainate/quisqualate-glutamate receptors [4]. Preventing the development of the reversible phase, concurrent blockers of the NMDA receptors also suppress the irreversible phase of continuous potentiation [5]. Thus, it is clear that the ability of nootropics to potentiate neuron reactions conditioned by NMDA-receptor activation can be the basis of their specific influence on memory and learning, as well as of their antiamnestetic effect.

LITERATURE CITED

1. I. I. Abramets, I. M. Samoilovich and I. V. Komissarov *Neirofiziologiya*, **23**, No. 6, 683-690 (1991).
2. T. A. Voronina, *Farmakol. Toksikol.*, **54**, No. 2, 6-10 (1991).
3. I. V. Komissarov, I. I. Abramets, and I. M. Samoilovich, *Dokl. Akad. Nauk SSSR*, **316**, No. 2, 501-503 (1991).
4. R. Anwyl, *Trends Pharmacol. Sci.*, **9**, No. 6, 236-239 (1989).
5. G. L. Collingridge, S. N. Davies, and K. G. Rayman, *J. Physiol.*, **414**, No 9, 23 (1989).
6. I. D. Forsyte and J. D. Clements J.D., *Ibid.*, **429**, No 10, 1-16 (1990).
7. I. Ito, S. Tanabe, A. Kohda, et al., *Ibid.*, **424**, No 5, 533-543 (1990).
8. F. Paoli, G. Spignoli, and G. Pepeu, *Psychopharmacology*, **100**, No. 1, 130-131 (1990).
9. F. Ponzio, P. Belfiore and L. Doriggotti, *Pharmacol. Res.*, **21**, suppl. No. 1, 103-104 (1989).
10. U. Stabuli, M. Kessler and G. Lynch, *Psychobiology*, **18**, No. 4, 377-381 (1990).