CR in the second phase of 15-HETE action involves potentiation of Ca^{2+} mobilization from the intracellular pools by 5-lipoxygenase eicosanoids via Ca^{2+}-and IP_3-dependent pathways.

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PHARMACOLOGY

Comparison of the Effects of Piracetam and N-Acetylaspartic Acid on Memory and on the Content of Transmitter Amino Acids in the Rat Brain during Simulation of a Neurotic State

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Recently, glutamic and aspartic acids as excitation transmitters have attracted the attention not only of neurobiologists but also of clinicians specializing in neuropsychiatry. These amino acids and their receptors have been found to be involved in the pathogenesis of a broad spectrum of diseases of the central nervous system (CNS), primarily of neurodegenerative states [2,4,6,7,10].

Studies of the properties of excitatory amino acid (EAA) receptors have shown that blocking of the latter may produce a therapeutic effect during ischemia, hypoxia, hypoglycemia of the brain, sei-

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TABLE 1. Content of Transmitter Amino Acids (μmol/g) in Brain Structures of Rats during Simulation of a Neurotic State ($M \pm m$)

Brain structure	Amino acid				
	glutamic	aspartic	GABA	glycine	taurine
	Control ($n=7$)				
Cerebral cortex	10.79±0.56	3.40±0.14	1.93±0.04	0.96±0.06	5.89±0.14
Hippocampus	9.15±0.54	2.79±0.11	2.20±0.10	1.22±0.08	6.04±0.11
	Neurotic state				
Cerebral cortex	9.65±0.34 (−11%)	3.45±0.11 (+4%)	2.73±0.12*** (+41%)	1.18±0.05* (+23%)	5.75±0.10 (−2%)
Hippocampus	11.61±0.20* (+27%)	2.76±0.09 (−1%)	2.82±0.09*** (+28%)	1.27±0.09 (+4%)	6.03±0.13 0

Note. Here and in Table 2: one, two, and three asterisks indicate $p<0.05$, $p<0.01$, and $p<0.001$, respectively; n = number of animals in the group.

zure syndrome, spasticity, emotional disturbances, and other pathological states [4,7,11].

Numerous data provide evidence that EAA and their receptors are involved in the formation of such fundamental processes as synaptic plasticity, long-term potentiation underlying learning and memory, regulation of the polyfunctional sensory systems of the brain, seizure threshold maintenance, muscle tone regulation, and physiological mechanisms of anxiety [7,10].

To date, the state of the EAA system during simulation of various brain pathologies, in particular, of an experimental neurotic state, has received no systematic study, nor has the possible therapeutic efficacy of nootropics under these conditions been examined.

The aim of the present study was to investigate the effect of piracetam and N-acetylaspartic acid, which exhibit nootropic properties [3], on memory and on the system of transmitter amino acids at a late stage of generation of a model neurotic state resulting from chronic stress.

MATERIALS AND METHODS

The experiments were carried out on 78 female rats weighing 180-210 g. The conditioned passive avoidance response (CPAR) was elaborated by a modified method [9], recording the movement of the animal from the light box (20×30 cm) into the dark box, where it received an aversive stimulation by alternating current (20-30 mA, 1 sec, 50 Hz), the strength of which was individually chosen in accordance with the vocalization threshold of the rats. After 24 h, CPAR preservation was tested, following which the group of experimental rats underwent neurotization daily during 1 month. In order to generate the neurotic state, a model of neuroergic stress, known as a "conflict of afferent excitations," was used [1]. Neurotization was performed in a computerized chamber with an electrode floor. At the final stage of neurotization (that is, three weeks after the beginning of simulation) the CPAR was tested, this making it possible to identify the group of rats with marked amnesia. Over the last week of neurotization, the animals of this group were administered piracetam (250 mg/kg, intraperitoneally) or N-acetylaspartic acid (NAA, 50 mg/kg, intraperitoneally) 1 hour prior to the stress session. After CPAR had been verified, the animals were decapitated, the brain was isolated, and the tissues were prepared for determination of transmitter amino acids (glutamic, aspartic, GABA, glycine, and taurine). The amino acid content in the cerebral cortex and hippocampus was determined with a T-339 amino acid analyzer by the method of ion exchange chromatography [6].

The experimental results were statistically processed using Student's test [5].

RESULTS

Neurotization was attended by the development of mnestic disturbances in 60% of animals, which was manifested as a disrupted CPAR. A number of changes in the state of the transmitter amino acid system were discovered in the brain structures of these animals (Table 1), this being reflected in an increased glutamate content (by 28%) in the hippocampus and an elevated GABA level in the cortex and hippocampus (by 41 and 28%, respectively, $p<0.01$). An increase of the glycine content (by 23%, $p<0.05$) was also noted in the cerebral cortex.

The administration of piracetam and NAA over the last 7 days of neurotization produced a protective effect against the mnestic disturbances in stressed animals. In this case, CPAR was preserved in 60% of rats receiving NAA versus 40% of animals in the control group ($p<0.05$). The effect of

TABLE 2. Effect of Piracetam and N-Acetylaspartic Acid Content of Transmitter Amino Acids (μmol/g) in Brain Structures of Rats for Simulation of a Neurotic State ($M \pm m$)

Brain structure	Amino acid				
	glutamic	aspartic	GABA	glycine	taurine
Piracetam, 250 mg/kg, i.p. ($n=7$)					
Cerebral cortex ($n=7$)	10.51±0.46 (+9%)	3.57±0.20 (+3%)	1.66±0.11*** (−39%)	0.60±0.04*** (−49%)	5.89±0.14*** (−34%)
Hyppocampus ($n=6$)	6.17±0.49*	2.15±0.14***	1.62±0.12***	0.60±0.04***	2.00±0.14***
NAA, 50 mg/kg, i.p.					
Cerebral cortex ($n=7$)	11.18±0.44* (+16%)	3.74±0.25 (+9%)	1.41±0.11*** (−48%)	0.99±0.09** (−16%)	4.92±0.11** (−14%)

piracetam was less marked: memory trace restoration was noted in just 25% ($p<0.05$).

In neurotized rats, piracetam and NAA caused marked changes of the content of transmitter amino acids (Table 2). For instance, while the content of glutamate and GABA in the hippocampus and of GABA and glycine in the cerebral cortex increased in experimental animals which received no drugs, the administration of piracetam to these animals resulted in a marked drop of the above values in the hippocampus and (for GABA and glycine) in the cerebral cortex as well. It is worthy of note that in this case the taurine content also proved to be markedly lower in both brain structures.

The effect of NAA manifested itself similarly with respect to the inhibitory amino acids GABA and glycine: their content dropped in the cerebral cortex. On the other hand, the glutamate level in the cortex proved to be slightly elevated (by 16%) in comparison with that observed in neurotized animals.

Thus, the trend of changes in the neurochemical profile of transmitter amino acids seems to be largely the same as for the effect of piracetam.

Of interest was the fact that piracetam was conducive to more marked alterations of the EAA indexes in the hippocampus vs. those in the cerebral cortex, this being in tune, on the one hand, with the important role of this brain structure in the generation of mnestic processes and, on the other hand, with the involvement of the EAA-ergic mechanisms in these processes [7,12].

Based on the suggestion that piracetam and NAA activate the brain cell metabolism and energetics [3,13], we used them to reveal their possible positive effect on the mnestic functions impaired due to neurotization.

Thus, our findings indicate that piracetam and NAA, substances with nootropic properties, are able to exert a positive effect upon memory during neurotization-provoked disturbances of conditioned-response activity. Our data on the influence of NAA on mnestic processes are consistent with the results of other scientists, who have noted a positive effect of NAA during amnesias of various genesis and during natural extinction of a habit [3]. It can be assumed that such an effect of NAA may be associated with an increased functional activity of neurons due either to enhancement of acetylation [8] or to a possible influence on lipid biosynthesis [3].

The effect of piracetam, which also prevents amnesia in CPAR, is in agreement with data on the antiamnestic efficacy of this group of substances [13], which presumably exert an influence upon one of the subtypes of glutamate receptors and effect changes in the ion channels of neuron membranes [12].

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