their subsequent recognition. Tranquilizers in minimal doses improve visual perception but impair it when the dose is increased; however, whatever the dose they never disturb completely the processes which lead ultimately to adequate response to external stimuli.

A parallel can thus be detected between the intensity of changes in visual stimulus analysis and the intensity of the hallucinogenic action of the drugs.

The intensity of the disturbances of subsequent stimulus analysis, which is closely linked with extrasensory factors [3, 6] during the action of hallucinogens and psychostimulants, and the absence of these disturbances during the action of tranquilizers, are particularly characteristic from this point of view. This fact is in good agreement with modern views on the origin of hallucinations, according to which they are not a disturbance of the functioning of an analyzer of any one particular modality, but they are connected with changes in the more general aspects of brain activity such as emotions and memory and figurative thinking [2].

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A GABA-ERGIC CORTICAL COMPONENT IN THE ACTION OF PIRACETAM AND THE CETYL ESTER OF GABA

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The high efficacy of piracetam in different types of psychoneurological pathology makes the study of the mechanism ofits action imperative. The ability of piracetam to exert a marked effect on memory functions has led to the suggestion that it acts on the cortex. To elucidate the possible role of GABA-ergic structures of the cortex in the mechanism of action of piracetam, it seemed a useful approach to analyze its effect by means of a test which the writers developed previously in order to detect GABA-ergic inhibition in the cortex, namely the recovery cycle of evoked cortical responses. The object of the present investigation was to use this test to study piracetam and its interaction with bicuculline, a blocker of GABA-ergic receptors, and with strychnine, a blocker of glycinergic receptors, and also to compare the effects of pracetam and the cetyl ester of GABA (CEGABA) — a compound whose GABA-mimetic effect was demonstrated previously [5, 8, 13]. It was also decided to study these substances from the point of view of their action on the main biochemical parameters of the GABA system: its level, and activity of enzymes of synthesis and deactivation.

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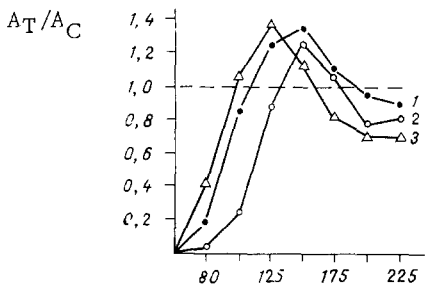

Fig. 1. Antagonism between piracetam and bicuculline in their action on recovery cycles of primary response of rat sensomotor cortex: 1) control; 2) 15 min after injection of piracetam (500 mg/kg, intraperitoneally); 3) 2 min after application of **bicuculline** (0.02% solution) to cerebral cortex and 20 min after injection of piracetam. Abscissa, intervals between conditioning and testing stimuli (in msec); ordinate, ratio between amplitudes of test and conditioning responses.

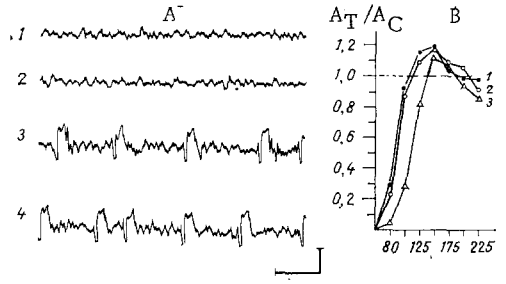

Fig. 2. Interaction between strychnine and piracetam in their effect on ECoG (A) and recovery cycle of primary response of **sensomotor cortex** (B) in rats. A: 1) Control; 2) 5 min after application of strychnine (0.017% solution) to sensomotor cortex; 3) the same after application of 0.051% strychnine solution; 4) 10 min after injection of piracetam (500 mg/kg, intraperitoneally) and 15 min after second application of strychnine. B: 1) Control; 2) 5 min after repeated application of strychnine (0.051% solution); 3) 10 min after injection of piracetam (500 mg/kg). Remainder of legend as in Fig. 1.

EXPERIMENTAL METHOD

Electrophysiological experiments were carried out on 25 noninbred male albino rats weighing 200-300 g, anesthetized with halothane for operations. The sciatic nerve was stimulated with paired pulses (0.3 msec, 1-2 V), the intervals between which varied from 80 to 300 msec. Primary responses of the sensomotor cortex were averaged in the course of the experiment on an LP 4840 (Nokia) multichannel analyzer. The ratio of the amplitude of the testing (second) and conditioning (first) responses was then calculated for each interval between stimuli and the corresponding graphs (recovery cycles) were plotted. Piracetam was injected intravenously, CEGABA intraperitoneally. Bicuculline and strychnine were applied to the cerebral cortex and injected intravenously. To assess the cortical effect of the drugs experiments were carried out on six cats with acute isolation of the cerebral cortex by Khananashvili's method [7]. The effect of the drugs on transcallosal responses was investigated in acute experiments on rabbits. Biochemical tests were carried out on male Wistar rats weighing 160-180 g. Activity of glutamate decarboxylase (GDC; E.C.1.15) was determined by a fluorometric method [11, 14], and aminobutyrate aminotransferase (GABA-T; E.C.2.6.1.19) by a colorimetric method [1]. The GABA content was determined by an electrophoretic method [12].

EXPERIMENTAL RESULTS

The results of the electrophysiological experiments showed that piracetam in doses of 250-500 mg/kg potentiates depression of the test potential when the interval between stimuli

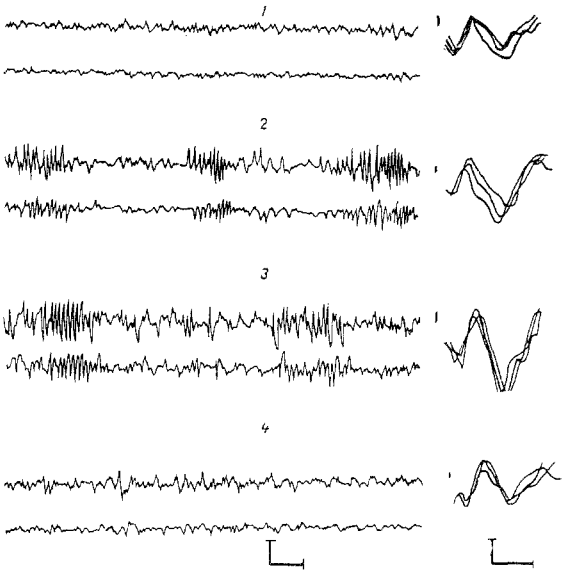

Fig. 3. Effect of CEGABA on ECoG and transcallosal response in rabbits. 1) Control; 2) 5 min; 3) 30 min; 4) 180 min after injection of CEGABA (10 mg/kg, intraperitoneally). Top trace recorded from somatosensory cortex, bottom trace from visual cortex. Calibration: 100 μV, 1 sec. Transcallosal responses recorded in right visual cortex in response to bipolar electrical stimulation of symmetrical point of left hemisphere shown on right. Each frame shows superposition of five responses recorded from oscilloscope screen. Calibration: 250 μV, 20 msec.

TABLE 1. Effect of Piracetam, CEGABA*, and Muscimol on Principal Parameters of the GABA System

Control	Dose, mg/kg	GABA 100±7	GDC 100±6	GABA-T 100±9
Piracetam	700 mg/kg	82±9 †	84±9	111±7
CEGABA	35 mg/kg	75±12†	—	105±17
Muscimol‡	0,6 mg/kg	92±13	85±16	96±4

Legend. *) Preparations injected intraperitoneally 30 min before determination; †) difference from control statistically significant at $P < 0.05$; ‡) data of Frey et al. [9].

is 80-125 msec in the recovery cycle of the first response (Fig. 1). The effects of piracetam in this test were similar to those of the GABA-T inhibitor Depakine (valproate) [3], and also of benzodiazepine tranquilizers that increase the sensitivity of cortical neurons to the inhibitory action of GABA [2, 6]. Depression of the test response was accompanied by synchronization of the ECoG. The action of the drug was manifested a few minutes after its injection and continued for a few hours. It could be interrupted by bicuculline, which specifically blocks GABA-ergic receptors, when applied to the cortex as a 0.02% solution (Fig. 1). The antagonism is two-way.

Because of the similarity between the side chain of piracetam and glycine, it was interesting to study the effect of the drug on the action of strychnine, blocking glycinergic receptors. It was found that strychnine, unlike bicuculline, does not cause changes in the recovery cycle reflecting weakening of inhibition in the cortex. It was shown that in order to provoke seizure discharges in the cortex by application to its surface, a higher concentration (approximately three times higher, calculated on the basis of molecular weight) of strychnine was needed compared with bicuculline (Fig. 2). Seizure discharges evoked by strychnine when administered systemically were not blocked by piracetam. The results are evidence of the specificity of the effects of piracetam on GABA-ergic inhibition. Preservation of the

synchronizing effect of the drug on the ECoG and of its antagonistic relations with bicucculline under isolated cortex conditions is evidence of the ability of piracetam to act directly on GABA-ergic processes in the cortex. CEGABA also has a similar action on the intensity of GABA-ergic inhibition in the intact and isolated cortex. Piracetam is known to increase the amplitude of the transcallosal response [10]. We showed that CEGABA also increases it. The difference is that CEGABA has a more marked synchronizing effect on the ECoG (Fig. 3).

The biochemical investigations also revealed similarity between piracetam and CEGABA (Table 1). A fall in the GABA level in the cerebral cortex was common to both substances. Accordingly it is an interesting fact that the standard GABA-mimetic muscimol also lowers the GABA concentration in the brain a little [9]. Considering the tendency for GDC activity to fall by a certain amount under the influence of these substances it can be postulated that GABA-mimetics activate a feedback mechanism, leading to a decrease in GABA synthesis. The data given above are evidence that piracetam and CEGABA can potentiate GABA-ergic inhibition. The difference between piracetam and CEGABA is that the effect of piracetam is mainly cortical in location, and is due either to the specific distribution of piracetam in the cortex [15] or to the special character of the cortical GABA-ergic receptors, which are more sensitive to the cyclic form of GABA than to its linear form. The absence of anticonvulsant activity in piracetam is probably explained by its inability to potentiate GABA-ergic inhibition in the rest of the brain. CEGABA, in the presence of a direct cortical effect, also has an influence on the midbrain reticular formation, the hippocampus [4], and the olfactory bulb [8]. This evidently explains the wide spectrum of neurotropic activity of CEGABA, which includes sedative and anticonvulsant effects, and also their absence in piracetam.

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