presynaptic nature and, correspondingly, with the presynaptic localization of $GABA_B$-receptors in the primordial hippocampus. This problem requires special investigation, for $GABA_B$-receptors in the mammalian hippocampus may evidently be postsynaptic in their location also [7]. Slowing of the action of baclofen in the primordial hippocampus after application of bicuculline in a high concentration may be associated with the relative sensitivity of the $GABA_B$-receptors to bicuculline [5].

The results of the present investigation confirm data of recent neuropharmacologic investigations showing the presence of two types of GABA receptors, at different levels of the vertebrate brain, with differences in their localization and the mechanism of their inhibitory action. The writers have shown for the first time that $GABA_B$-receptors are present in the olfactory bulb, so that the concrete mechanisms of presynaptic inhibition in this structure can be identified. The presence of $GABA_B$-receptors in the primordial hippocampus enables the question of the presence of presynaptic inhibition in this forebrain structure of the Anura to be subjected to examination.

LITERATURE CITED

1. G. S. Voronkov and E. G. Gusel'nikova, Zh. Vyssh. Nerv. Deyat., 17, 744 (1967).
2. K. G. Gusel'nikova, G. S. Voronkov, L. E. Tsitolovskii, and V. V. Engovatov, Zh. Vyssh. Nerv. Deyat., 20, 649 (1970).
3. S. E. Margolis, Dokl. Akad. Nauk SSSR, 190, 729 (1970).
4. A. A. Potapov, Neirofiziologiya, 15, 88 (1983).
5. L. K. Rägo, A. M. Nurk, and H. A. Sarv, Uch. Zap. Tartu Univ., No. 687, 17 (1984).
6. V. V. Trepakov and S. A. Saakyan, in: Abstracts of Proceedings of the 9th All-Union Conference on Biochemistry of the Nervous System [in Russian], Erevan (1983), p. 243.
7. B. Ault and J. V. Nadler, Br. J. Pharmacol., 80, 211 (1983).
8. K. Beaumont, W. S. Chilton, H. J. Jamamura, and S. J. Enna, Brain Res., 148, 153 (1978).
9. N. G. Bowery, D. R. Hill, A. L. Hudson, et al., Nature, 283, 92 (1980).
10. F. V. De Feudis, Neurochem. Intern., 5, 175 (1983).
11. S. J. Enna, J. Collins, and S. Snyder, Brain Res., 124, 185 (1977).
12. D. R. Hill and N. G. Bowery, Nature, 290, 149 (1981).
13. C. E. Jahr and R. A. Nicoll, J. Physiol. (London), 318, 375 (1981).
14. E. Mann and S. J. Enna, Brain Res., 184, 367 (1980).
15. M. C. Nowycky, K. Mori, and G. M. Shepherd, J. Neurophysiol., 46, 639 (1981).

SPECIFICITY OF ACTION OF PYRACETAM, PYRITINOL, AND CLEREGIL ON THE TRANSCALLOSAL EVOKED POTENTIAL

T. A. Voronina, S. V. Krapivin, and L. N. Nerobkova

UDC 615.214.22.015.4:612.82].07

KEY WORDS: nootropic drugs, transcallosal evoked potential

Drugs with nootropic action affect the mental functions and many integrative processes of the brain, but do not exhibit psychotropic activity as revealed by a number of commonly used pharmacologic tests [3, 9-11]. Considering the data on the important role of the corpus callosum in learning and memory [4, 5], it can be postulated that the transcallosal evoked potential (TEP) is one of the most informative parameters for analysis of the specificity of the effect of drugs with a nootropic action, and which improve memory.

The aim of this investigation was to undertake a comparative study of the effect of drugs with a nootropic type of action on the TEP of the rabbit brain.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow.

(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 101, No. 3, pp. 320-322, March, 1986. Original article submitted April 29, 1985.

0007-4888/86/0003-0326$12.50

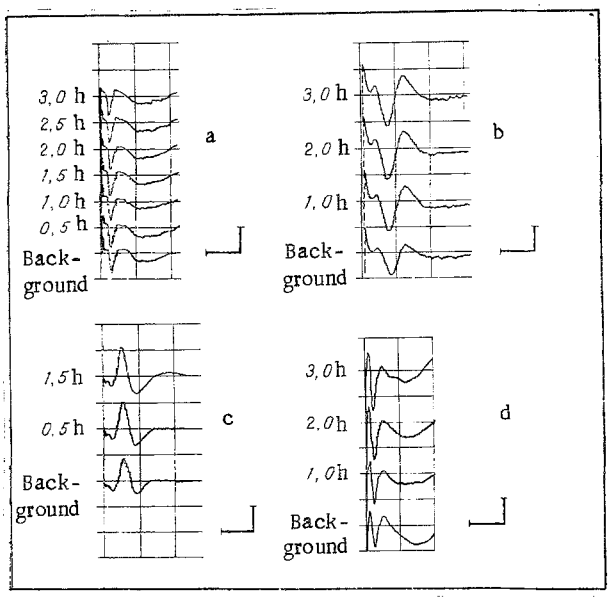

Fig. 1. TEP of rabbit brain before and after injection of physiological saline (a), pyracetam (b), pyritinol (c), positivity upward from zero line), and cleregil (d). From bottom to top: averaged EP for 20 realizations, recorded consecutively in time before (background) and after injection of drugs. Doses (in ng/kg): pyracetam 300, pyritinol 100, cleregil 50. Calibration: A, D) 200 μV, 50 msec; B, C) 200 μV, 20 msec.

EXPERIMENTAL METHOD

Experiments were carried out on 47 noninbred rabbits. The animals were scalped under procaine anesthesia and a bipolar stimulating electrode implanted into the precentral region of the cortex of one cerebral hemisphere. The recording monopolar electrode was located at the symmetrically opposite point of the other hemisphere. The reference needle electrode was implanted into the occipital scar tissue on the rabbit's head. Experiments were carried out 5 or 6 days after the operation, on unanesthetized, uncurarized animals, lightly fixed by their limbs in a special frame.

The TEP (interhemispheric, transcortical evoked potential — EP) was obtained by electrical stimulation (23-40 V, 0.2-1.0 msec). The threshold of EP was found first, and the action of the substances was tested during stimulation at a strength equal to 1.5 times the strength of the threshold stimulus.

The EP, averaged for 20 realizations, was recorded for 500 msec after application of the stimulus. Component analysis of the TEP was carried out, with estimation of latent periods, amplitude, and shape of the first positive (P_1), first negative (N_1), and second positive (P_2) components of the EP and their changes following administration of the substances.

The data were recorded and analyzed by means of a BASIS Neurocomputer Analyzer (OTH Biomedica, Italy). The drugs used for testing were: pyracetam (Nootropil, 50-1000 mg/kg, from Polfa, Poland); pyritinol (Encephabol, 50-200 mg/kg, from Merck, West Germany); cleregil (10-200 mg/kg, from Merck-Clevenot, West Germany). The drugs were injected intraperitoneally and their effect was studied for several hours after injection.

EXPERIMENTAL RESULTS

The TEP recorded had the following characteristics: the average latent period of P_1 was 13 ± 1 msec with an amplitude of 100 to 400 μV, the latent period of N_1 was 26 ± 4 msec, with an amplitude from 50 to 200 μV, and the latent period of P_2 was 70 ± 12 msec, with an amplitude from 50 to 250 μV.

The TEP of the animal's brain before injection of the drug served as the control. A group of six rabbits into which physiological saline was injected under identical conditions served as the additional control.

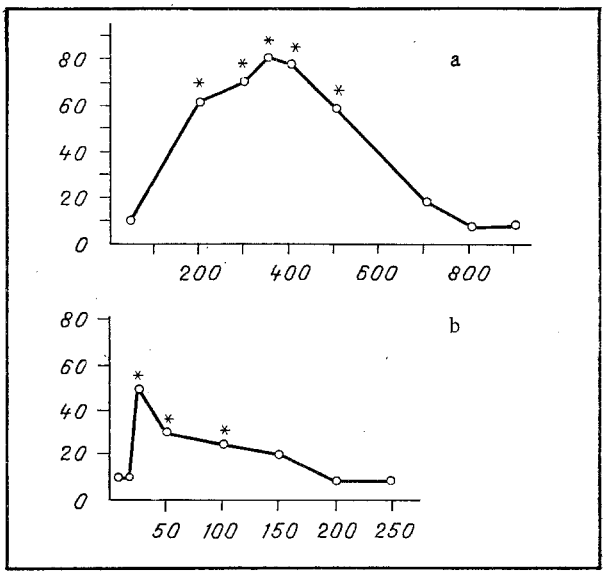

Fig. 2. Increase in total amplitude ($P_1 + N_1$) of TEP depending on dose of pyracetam (A) and cleregil (B). Abscissa, doses (in mg/kg); ordinate, increase in amplitude (in %).

Injection of physiological saline caused no changes in TEP (Fig. 1). Fluctuations in the amplitude of its components reached 10%, in either the upward or the downward direction, in the course of several hours; the greatest variations in the amplitude of EP were observed in the first 30-40 min after injection. The latent periods and shape of the components of TEP were unchanged. All the drugs with nootropic action which were studied, namely pyracetam, pyritinol, and cleregil, were found to have a marked facilitatory effect on TEP. A study of the dose-effect curve for the drug showed that the increase in amplitude of TEP was dose-dependent and biphasic in character. For instance, with an increase in the dose of pyracetam from 50 to 400 mg/kg a gradual increase in the effect was observed; however, in response to a further increase in dose the effect decreased and almost completely disappeared when 800-1000 mg/kg of pyracetam was given (Fig. 2). Cleregil also has a similar biphasic type of dose-effect curve.

In the second stage of the work, in order to demonstrate specific features of the action of the nootropic drugs, their effect on different components of the TEP was investigated. In these investigations the substances were used in maximal active doses.

Component analysis of the TEP under the influence of drugs with a nootropic action showed that they did not affect the latent periods of components P_1, N_1, and P_2. However, the drugs showed specific features in their action on the amplitude of the components of EP (Fig. 1). For instance, pyracetam increased the amplitude of all components tested by 60-70%. Pyritinol also increased the amplitude of all components, but by a lesser degree — by 25-30%. Compared with these preparations cleregil had a varied action on the amplitude of the components of TEP. Against the background of an increased amplitude of the first positive wave P_1, there was a decrease in amplitude of the first negative wave N_1; the total amplitude of $P_1 + N_1$ was increased to 30-40%. The second positive wave P_2 in some cases was reduced, in others increased in amplitude.

Thus in the group of psychotropic drugs with nootropic action differences were found in their effect on the components of TEP (Table 1).

In the modern view, the genesis of the positive components of EP is based on activity of nerve cells in deep layers of the cortex, whereas genesis of the negative component is based on activity of nerve cells in the higher layers of the cerebral cortex [1]. The first positive and negative components of the TEP have been shown to owe their origin to the passage of excitation from the stimulated area of the cerebral cortex to that recorded directly through the corpus component, known in the literature also as the "late interhemispheric response," is polysynaptic and extracallosal. It owes its origin to the passage of excitation not through the corpus callosum, but through the mesencephalic reticular formation [12, 13]. It is this late interhemispheric response which cannot be analyzed in anesthetized animals [13].

TABLE 1. Effect of Drugs with Nootropic Type of Action on Different Components of TEP

Substance	Dose, mg/kg	P_1	N_1	P_1+N_1	P_2
Pyracetam	300—500	++	++	++	++
Pyritinol	100—150	+	+	+	+
Cleregil	25—50	++	—	+	±

Legend. ++) Increase in amplitude by more than 50%, +) increase in amplitude by under 50%, —) decrease in amplitude.

We also know that different cortical neurons [4, 6] participate in generation of components P_1 and P_2, relations between which are evidently mutually antagonistic [2].

A common feature of the drugs with nootropic action which were investigated is thus the fact that they do not affect the latent periods of the components of TEP and they increase the total amplitude of $(P_1 + N_1)$, i.e., the amplitude of the true transcallosal response. This suggests that the neurophysiological mechanism of the action of these substances is evidently connected with facilitation of the transmission of information between the cerebral hemispheres, which leads to an improvement in integrative activity of the brain.

LITERATURE CITED

1. V. I. Gusel'nikov, Electrophysiology of the Brain [in Russian], Moscow (1976).
2. T. M. Mamonets, Fiziol. Zh., No. 5, 617 (1984).
3. M. D. Mashkovskii, L. F. Roshchina, and A. I. Polezhaeva, Farmakol. Toksikol., No. 6, 676 (1977).
4. V. M. Mosidze, R. S. Rizhinashvili, N. K. Totibadze, et al., The Split Brain [in Russian], Tbilisi (1972).
5. V. M. Mosidze, R. S. Rizhinashvili, Z. V. Samadashvili, and R. I. Turashvili, Functional Asymmetry of the Brain [in Russian], Tbilisi (1977).
6. V. M. Okudzhava, Basic Neurophysicological Mechanisms of Epileptic Activity [in Russian], Tbilisi (1969).
7. H. T. Chang, J. Neurophysiol., 16, 133 (1953).
8. B. Gratstein, J. Neurophysiol., 22, 504 (1959).
9. C. Giurgea, Conditioned Reflex, 8, 108 (1973).
10. C. Giurgea, in: Biological Psychiatry Today, J. Obiols et al., eds., Vol. B-2, Amsterdam (1979), pp. 876-881.
11. C. Giurgea and F. Moyersoons, Arch, Int. Pharmacodyn., 199, 67 (1972).
12. L. Rutledge and T. Kennedy, J. Neurophysiol., 23, 188 (1960).
13. L. Rutledge and T. Kennedy, Exp. Neurol., 4, 470 (1961).