EFFECT OF OXIRACETAM AND PIRACETAM ON CEREBRAL CORTICAL UNIT ACTIVITY

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Oxiracetam (4-hydroxy-2-oxo-1-pyrrolidineacetamide), a piracetam analog, was synthesized in 1974 and is currently in clinical use as a nootropic agent [4, 5]. However, the mechanism of action of this compound has not been adequately studied and, in particular, there is virtually no information in the literature on its effect on electrical activity of single neurons in different parts of the mammalian brain. One of the aims of the present investigation was accordingly to study the action of oxiracetam and to compare it with that of the classical nootropic agent piracetam, on unit activity in the cerebral cortex. Another aim was to study the possible antagonism of nootropic agents and opioids at the neuronal level, for the writers showed previously on various behavioral models (analgesia, vomiting, catalepsy) that such antagonism exists [1, 2].

EXPERIMENTAL METHOD

Experiments were carried out on curarized animals (11 male rabbits weighing 2.3-2.5 kg and seven male cats weighing 3.1-3.6 kg). maintained on artificial ventilation of the lungs. The animals' body temperature was kept constant by means of an electric heater. The preliminary surgical manipulations (tracheotomy, scalping, etc.) were performed under general anesthesia (pentobarbital sodium, 40 mg/kg. intraperitoneally). Multibarreled glass microelectrodes, described by the writers previously [3], were used to record extracellular single unit activity (the neurons began to be recorded 12-14 h after injection of the pentobarbital) and microiontophoretic application of the nootropic agents and opioids. Information on spontaneous unit activity was processed on an Élektronika DZ-28 or DVK-2 microcomputer. For microiontophoresis the following freshly prepared solutions were used (the solvent was 0.03 M NaCl): oxiracetam 0.5 M, pH 5.0 (synthesized in the Research Institute of Biomedical Technology Ministry of Health of the USSR), piracetam 0.5 M, pH 5.0, morphine hydrochloride 0.05 M, pH 5.0, and (D-Ala^2,D-Leu^5)-enkephalin (DADLE, peptide synthesized at the All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR), 0.02 M, pH 4.0. The recording and compensating barrels of the microelectrode were filled with 3 M NaCL solution. The substances were expelled by currents of positive polarity, with a strength of 10-60 mA. Somatosensory area I (the focus of maximal activity of the sciatic or radial nerve) of the cerebral cortex was chosen for investigation.

EXPERIMENTAL RESULTS

The results of the microiontophoretic investigation are given in Table 1. They show that oxiracetam and piracetam had an about equal effect on spontaneous unit activity in somatosensory area I of the cerebral cortex. For example, in both cases the percentage of nerve cells responding to microiontopohretic application of the drug was virtually identical (71% for oxiracetam, 68% for piracetam). The nootropic agents (Table 1, Fig. 1) predominantly caused inhibition of spontaneous unit activity (oxiracetam reduced the discharge frequency in 58% of neurons, piracetam in 53%. The excitatory effects of the drugs were much less frequently found than inhibitory: in 13% of cases for oxiracetam, in 16% for piracetam. Opposite responses to application of oxiracetam and piracetam likewise were not observed on the same neurons, i.e., if the response of the nerve cell to microiontophoretic application of oxiracetam was inhibitory (excitatory), it responded in the same way to application of piracetam.

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TABLE 1. Effect of Oxiracetam and Piracetam on Spontaneous Unit Activity in Somatosensory Area I of the Cerebral Cortex

Preparation	Total number of neurons	Excitatory effect	Inhibitory effect	No effect
Oxiracetam	3[illegible]	4	18	9
Piracetam	38	6	*	12
Morphine	38	5	*	17
DADLE	35	4	*	6

*Text missing in Russian Original – Publisher.

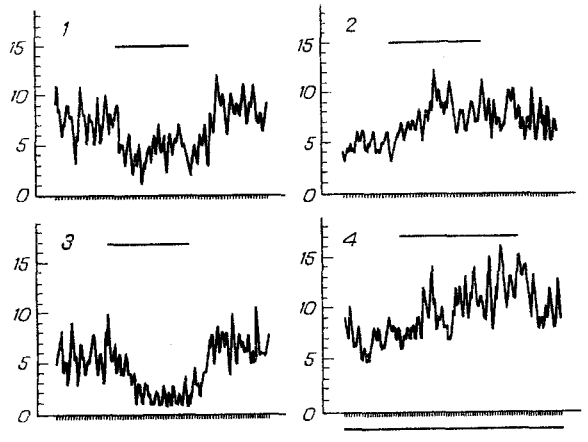

Fig. 1

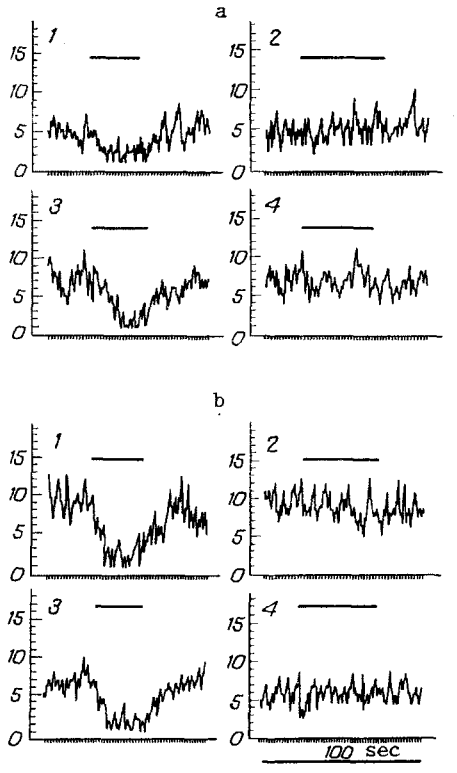

Fig. 2

Fig. 1. Effect of nootropic drugs on spontaneous unit activity in somatosensory area I of the cat cerebral cortex. 1, 2, and 4) Different neurons. 1) Piracetam (50 mA), 2) piracetam (50 mA), 3) oxiracetam (50 mA), 4) oxiracetam (50 mA). Horizontal line above histograms indicates time of electrophoresis of drugs. Calibration: abscissa: 100 sec; ordinate, 15 spikes/sec.

Fig. 2. Blocking of depressant action of opioids on spontaneous unit activity by nootropic drugs. A) Effect of piracetam: 1) morphine (50 mA), 2) morphine (50 mA) preceded by piracetam (50 mA), 3) DADLE (40 mA), 4) DADLE (40 mA) preceded by piracetam (50 mA), 5) effect of oxiracetam: 1) morphine (50 mA), 2) morphine (50 mA) preceded by oxiracetam (50 mA), 3) DADLE (50 mA), 4) DADLE (50 mA) preceded by oxiracetam. Remainder of legend as to Fig. 1.

So far as opioids are concerned, morphine and DADLE had a similar effect on spontaneous cortical unit activity. Mainly a depressant effect was observed (Table 1, Fig. 1; morphine reduced the discharge frequency in 42% of neurons, DADLE did so in 43%).

Investigation of interaction between nootropic drugs and opioids revealed (Fig. 2) that preliminary application of oxiracetam sometimes blocked the inhibitory action of both morphine (in two of 13 cases) and DADLE (in two of nine cases). Piracetam had a similar action (abolition of the depressant effect of morphine in two of 12 cases, of DADLE in one of 10 cases). No differences were found during interaction of the new-agonist morphine and the

δ-agonist DADLE with the nootropic drugs. Thus the results of this microionotophoretic study lead to the following conclusion. First, a high proportion of cerebral cortical neurons (about 70%) is sensitive to nootropic drugs, and this may lie at the basis of the mechanism of their action on the higher integrative functions of the brain. Second, among cerebral cortical neurons there is a small cell population on which antagonistic relations are exhibited between nootropic drugs and opioids.

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STUDY OF GABA-BENZODIAZEPINE RECEPTOR SYSTEMS OF THE HUMAN MYOMETRIUM

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Tocolytics of the β_2-adrenomimetic group and inhibitors of prostaglandin synthesis, used at the present time, have not solved the problem of treatment and prevention of the premature termination of pregnancy, and moreover, their adverse action on mother and fetus has been demonstrated [3, 4]. A search for new drugs with a more physiological mechanism of action, for the protection of pregnancy, and created on a basis of endogenous biologically active substances, is therefore necessary.

In the modern view, gamma-aminobutyric acid (GABA) is the leading neurotransmitter of inhibition in the CNS [1, 2] and at the periphery [6, 8, 9]. It has been suggested that GABA-positive drugs with an inhibitory type of action may be used as agents for the pathogenic treatment and prevention of threatened abortion, coexisting with GABA-deficient states. However, only sporadic studies of GABA-benzodiazepine (BD) receptor systems of the myometrium have been reported in the literature [5, 7, 11]. The existence of GABA-BD complexes in the human myometrium had not hitherto been studied. The aim of this investigation was to determine sites of specific binding of ^{14}C-GABA and ^{3}H-flunitrazepan in the plasma membranes (PM) of the human myometrium, and also to study the possibility of linking of these sites.

EXPERIMENTAL METHOD

Tissue from the histologically unchanged human myometrium, obtained in the course of hysterotomy for myoma, was used. The PM fraction was obtained by differential centrifugation and stepwise sucrose gradient followed by repeated washing [10]. The purity of the isolated PM fraction was estimated by enzyme analysis. To determine binding parameters of ^{14}C-GABA ("Amersham") and ^{3}H-flunitrazepam ("Amersham") with PM the labeled compounds were incubated, within the concentration range of 10-300 mM with 0.1 ml of a suspension of PM (1 mg/ml as protein) at 4°C for 2 h. At the end of incubation PM were precipitated on CF/F

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