EFFECT OF OXYMETHACIL ON THE MICROCIRCULATION AND CEREBRAL CORTICAL SINGLE UNIT ACTIVITY IN CATS WITH ACUTE PHOSPHACOL POISONING

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Organophosphorus compounds (OPC) cause disturbances of the blood supply and electrical activity of the brain [6, 9]. It has been suggested that, besides the anticholinesterase mechanism of the toxic action of OPC, an important role is played also by stimulation of lipid peroxidation (LPO) [7, 8]. Much attention is currently being paid to the study of the effect of antioxidants on the metabolism and functional state of the various systems of the body during exposure to extremal factors, induced by toxic agents [14]. It has been shown that hydroxy-derivatives of uracil possess marked antioxidative properties [3].

The aim of this investigation was to study the prophylactic action of 6-methyl-5-hydroxyuracil (oxymethacil, OM) on important parameters of cerebral cortical function in cats, namely the microcirculation and single cortical unit activity under conditions of severe phosphacol poisoning.

EXPERIMENTAL METHOD

Experiments were carried out on male cats weighing 3-3.5 kg, superficially anesthetized with pentobarbital (30 mg/kg), immobilized with tubocurarine, and artificially ventilated. The time course of single unit activity (SUA) of the sensomotor region of the cerebral cortex was studied by means of extracellular metallic microelectrodes, by two methods. In the main part of the experiments the number of spontaneously active neurons recorded during insertion of the microelectrode from the surface of the cerebral cortex to a depth of 2 mm, was determined at chosen test time intervals (two or three measurements at each). In some experiments, single unit activity was recorded continuously before and after administration of drugs. Synchronously with the recording of SUA, changes in the microcirculation in blood vessels of the cortical gray matter were assessed. For this purpose, the structures of a living preparation of the sensomotor cortex with its blood supply preserved were subjected to intravital microscopy, using the Lyumam KF-1 contact microscope and a "Sony" video television system. Details of the method used to obtain the living preparation and its microscopic examination were described previously [4]. Changes in the microcirculation in the visible blood vessels (arterioles, venules, capillaries; 8-10 microvessels in each experiment) of the cortical preparation were assessed by the method suggested in [11], which enables the dynamics of the microcirculation in separate blood vessels to be assessed qualitatively on a 5-point scale: 5) initial level of blood flow, 4) moderate slowing of blood flow with less frequent passage of portions of blood cells, 3) marked slowing of the blood flow with detection of single blood cells, and 2-1) pendulum-like movement, cessation of the blood flow. The blood pressure (BP) was recorded by a direct method involving catheterization of the femoral artery, using the Soviet PPV-02 pneumatopressovasometer. Phosphacol (0.8 mg/kg) and the pharmacological agents benactyzine (0.5 mg/kg) and oxymethacil (5.0 mg/kg) were injected intravenously.

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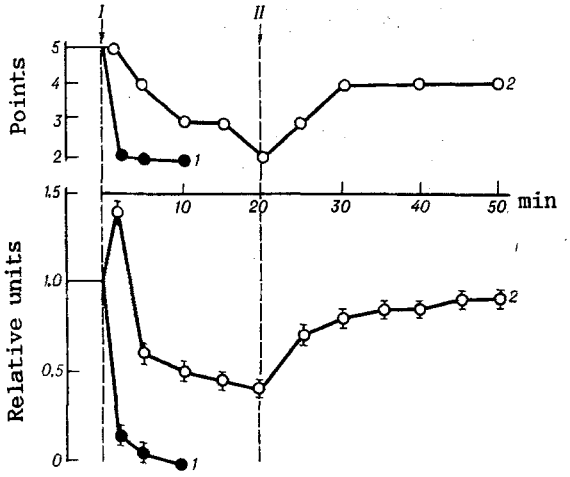

Fig. 1. Dynamics of cerebral cortical microcirculation and blood pressure after injection of phosphacol (I) and benactyzine (II). Abscissa, time of experiment (in min); ordinate: above — microcirculation (in points); below — blood pressure (in relative units, circles represent arithmetic mean ± standard error from eight experiments). 1) Effect of phosphacol, 2) effect of phosphacol preceded by OM.

EXPERIMENTAL RESULTS

There were two series of experiments (with eight animals in each series). In series I the effect of phosphacol on the time course of the recorded parameters was studied. In series II, OM was given 60 min before injection of phosphacol. In both series benactyzine was used as therapeutic agent, and was injected into the animals until the maximal effect of phosphacol on the test parameters was achieved.

In the experiments of series I a sharp fall of BP, profound changes in the microcirculation in the cerebral cortical vessels, and in some cases cessation of the blood flow were observed 2 min after injection of phosphacol (Fig. 1). Immediately after short-term activation of SUA, it was inhibited (Fig. 2). Spontaneously active neurons were not discovered 5 min after injection of phosphacol. Benactyzine had no therapeutic action: levels of BP, the microcirculation, and SUA were not restored to their original values.

In the experiments of series II when OM was given prophylactically, phosphacol caused less severe and later changes in the test parameters. A steep drop of BP and cessation of the blood flow in the cerebral cortical vessels were not recorded until the 20th minute of poisoning (Fig. 1). SUA was inhibited after 10 min but continued to be detected in individual neurons until the blood flow ceased (Figs. 2 and 3). Injection of benactyzine was accompanied by elevation of BP and improvement of the microcirculation, but recovery of these parameters was incomplete (Fig. 1). Against this background the appearance of SUA was observed at the 5th-10th minute, followed by the development of hyperactivation and by an increase in the number of spontaneously active neurons compared with initially (Figs. 2 and 3).

The results are evidence that disturbances of cerebral cortical function, expressed as inhibition of SUA, developing rapidly in the presence of a severe degree of phosphacol poisoning, may be due to sudden disturbances of the hemodynamics, leading to ischemia of the nerve cells. Under these conditions the use of the muscarinic cholinolytic benactyzine had no therapeutic effect.

When the antioxidant OM was used prophylactically it was found to have a protective effect on phosphacol-induced changes in the hemodynamics and cerebral cortical unit activity.

This effect was clearly manifested when a combination of OM and the muscarinic cholinolytic benactyzine was given to animals with phosphacol poisoning.

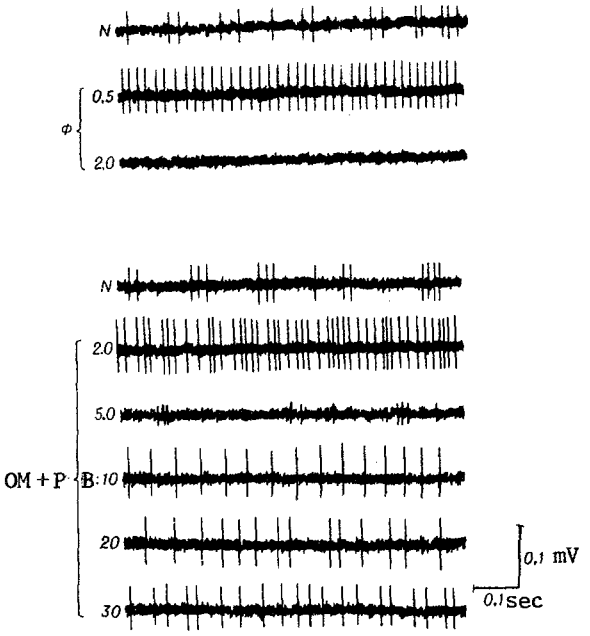

Fig. 2. Typical traces of spike discharges showing effect of phosphacol (P) and phosphacol preceded by oxymethacil (OM + P), followed by injection of benactyzine (B).

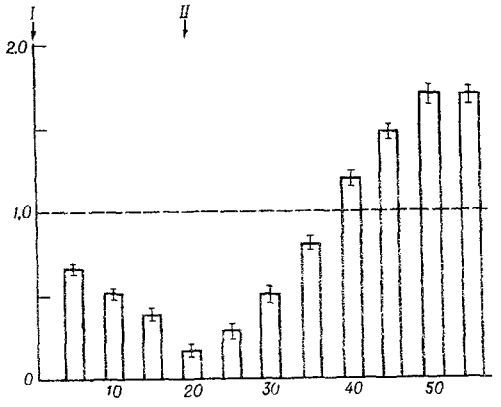

Fig. 3. Time course of number of spontaneously active cerebral cortical neurons in experiments with injection of phosphacol preceded by OM. Abscissa, time of experiment (in min); ordinate, number of spontaneously active neurons (in relative units); broken line — their initial number. I) Injection of phosphacol; II) injection of benactyzine. Columns represent arithmetic mean values ± standard error (n = 18).

The results of these experiments supplement the existing information on mechanisms of action of OPC. They indirectly confirm the view that LPO plays an important role in the pathogenesis of OPC poisoning. Initiation of this process by organophosphorus compounds may be connected both with their direct action on neuron membranes [13] and with the ischemic factor which, as we know, facilitates the development of LPO in brain tissues [10, 12].

The discovery that SUA can be restored through the prophylactic action of OM after a relatively long period of disturbance of the cerebral cortical blood supply by phosphacol is evidence of the protective effect of OM on the electrogenic properties of the neuronal plasma membrane, evidently due to its antioxidant-dependent stabilization [5]. In the modern view, changes in LPO activity can lead to modification of the properties of different membrane receptors [1, 2].

Consequently, the positive effect of the muscarinic cholinolytic benactyzine when given against the background of prophylactic administration of OM and subsequent phosphacol poisoning, may perhaps be connected with the direct action of the antioxidant on the properties of muscarinic acetylcholine receptors.

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