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EXPERIMENTAL STUDY OF THE ANTIHYPOXIC PROPERTIES OF IBUPROFEN AND OTHER NONSTEROID ANTIINFLAMMATORY AGENTS

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KEY WORDS: hypoxia; ibuprofen; orthofen; nonsteroid antiinflammatory agents; inhibitors of prostaglandin biosynthesis.

The pathogenesis of hypoxic states includes several stages, some of them connected with disturbance of the function of the arachidonic acid cascade and with the formation of a number of icosanoids (prostaglandins — PG, prostacycline, thromboxanes, etc.) [2]. In view of data showing that PG can cause disturbances of vascular resistance, which plays an essential role in hypoxic states [3, 6], it was interesting to study the action of various inhibitors of PG biosynthesis, namely nonsteroid antiinflammatory agents (NSAIA) such as ibuprofen, orthofen (diclofenac sodium), acetylsalicylic acid (aspirin), and butadione, on various models of experimental hypoxia.

EXPERIMENTAL METHOD

The effect of NSAIA on the survival time of animals was studied on a model of acute hypoxic hypoxia with hypercapnia [1], using noninbred male albino mice weighing 20-22 g. Each mouse was placed in a vessel with a capacity of 250 ml, with an airtight lid. The presence of an antihypoxic effect was judged by the change in survival time of the mice (in minutes) in the airtight chamber compared with the control. The drugs were given internally and intra-

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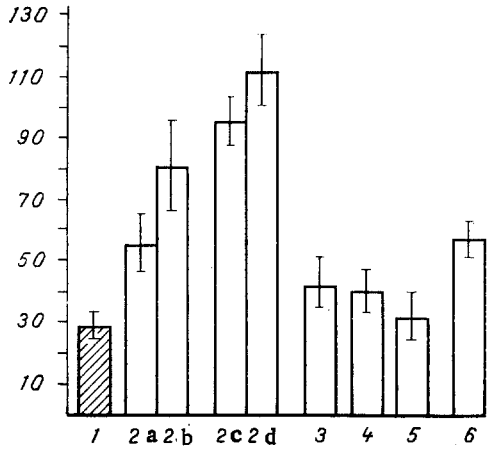

Fig. 1. Effect of ibuprofen and other NSAIA compared with that of sodium hydroxybutyrate on the survival time of mice (in min) in an airtight chamber. 1) Control; 2) ibuprofen: a) 250 mg/kg, internally, b) 250 mg/kg, intraperitoneally, c) 500 mg/kg, internally, d) 500 mg/kg intraperitoneally; 3) orthofen, 250 mg/kg, internally; 4) aspirin, 500 mg/kg, internally; 5) butadione, 500 mg/kg internally; 6) sodium hydroxybutyrate, 100 mg/kg, intraperitoneally.

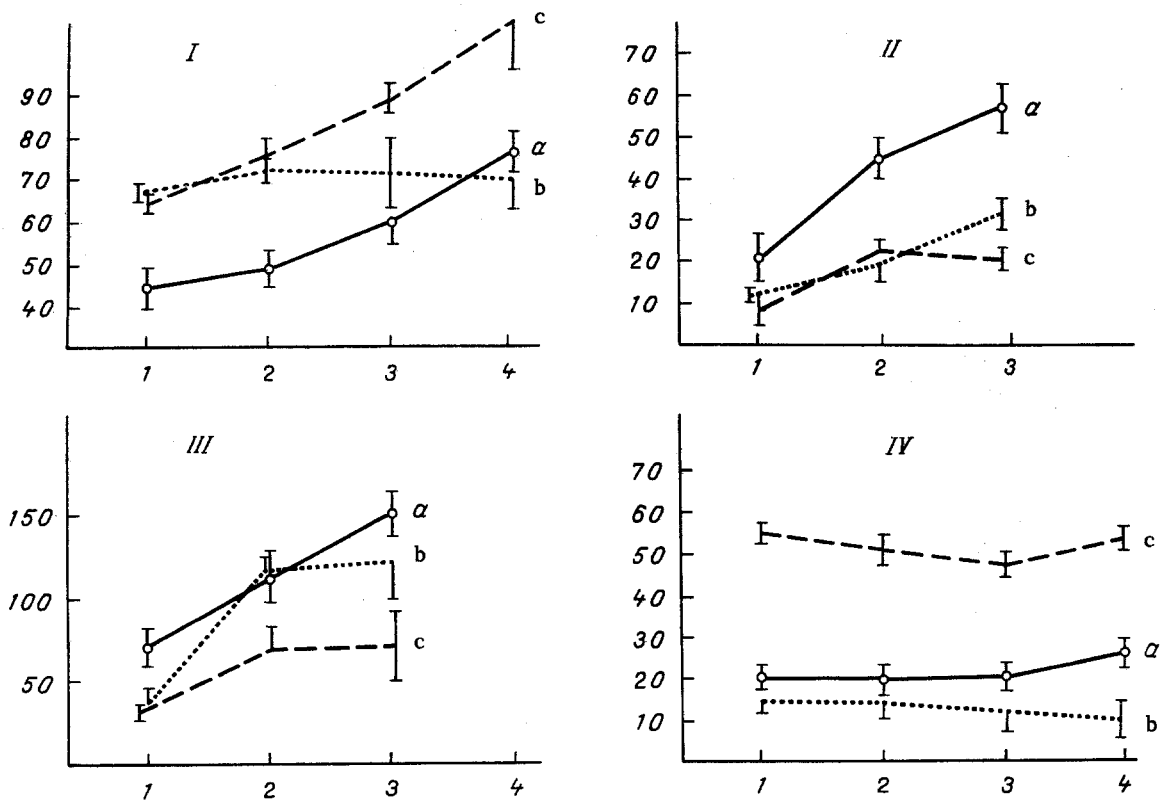

Fig. 2. Effect of orthofen and ibuprofen on resistance of the rat brain to asphyctic hypoxia. Abscissa, number of anoxic episodes; ordinate, time (in sec). 1) Time before disappearance of ECoG; II) time before resumption of ECoG; III) total time of electrical cortical silence; IV) time before beginning of bradycardia. a) Control; b) administration of orthofen; c) administration of ibuprofen.

peritoneally in doses of 25, 50, 100, 250, and 500 mg/kg (except orthofen, the highest dose of which was 250 mg/kg), 60 min before the animals were placed in the airtight chamber. Activity of the drugs was compared with the action (intraperitoneal injection) of sodium hydroxybutyrate in a dose of 100 mg/kg (Senior Scientific Assistant L. F. Roshchina took part in these investigations).

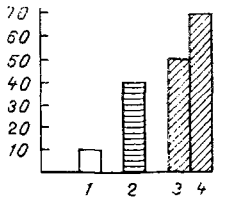

Fig. 3. Effect of orthofen and ibuprofen on resistance of rats to circulatory cerebral hypoxia. Ordinate, number of surviving animals (in %). 1) Control; 2) orthofen; 3) ibuprofen; 4) sodium salt of ibuprofen.

Asphyctic hypoxia was produced by the method in [5] on noninbred male rats weighing 180-220 g. The animals, immobilized with succinyl choline (10 mg/kg, intravenously) were connected to an artificial respiration apparatus and hypoxia was induced by repeated disconnection of the artificial ventilation at intervals of 10 min for 90, 120, 150, and 180 sec. The electrocorticogram (ECoG) and the ECG were recorded. Ibuprofen (250 mg/kg) and orthofen (200 mg/kg) were injected intraperitoneally 1 h before the experiment.

Circulatory hypoxia was induced in Wistar rats of the same sex and same body weight by bilateral ligation of the common carotid arteries. Ibuprofen and orthofen (250 and 200 mg/kg, respectively) were injected intraperitoneally immediately after the operation. Any antihypoxic properties of the drugs were revealed by an increase in the survival rate of the animals 24 h after ligation of the vessels.

The experimental results were subjected to statistical analysis with calculation of the arithmetic mean values and their comparison by Student's t test.

EXPERIMENTAL RESULTS

Starting with a dose of 250 mg/kg (internally or intraperitoneally) ibuprofen lengthened the survival time of the mice in a model of hypoxic hypoxia with hypercapnia. In the control the survival time was 29.3 (24.1-34.5) min, after preliminary internal administration of ibuprofen in a dose of 250 mg/kg it was 55.0 (44.4-66.6) min, and after intraperitoneal injection of the same dose it was 71.6 (61.6-81.6) min ($p < 0.01$). If ibuprofen was given in a dose of 500 mg/kg the survival time of the animals was 95.5 (71.0-120.0) min by internal, and 116.5 (107.4-134.6) min by the intraperitoneal route. Meanwhile orthofen, aspirin, and butadione, in the same doses, had no significant effect on the survival time of the animals in the airtight chamber. The action of sodium hydroxybutyrate in a dose of 100 mg/kg under these experimental conditions was comparable with the action of ibuprofen (Fig. 1).

On a model of asphyctic hypoxia in rats ibuprofen and orthofen gave an antihypoxic effect: it increased the duration of the period before disappearance of the ECoG in response to anoxia and accelerated restoration of cerebral cortical function after reduction of artificial respiration. The activity of ibuprofen was greater than that of orthofen (Fig. 2), which was active mainly in the 1st and 2nd anoxic episodes.

The time course of the changes in the total duration of cortical electrical silence was similar under the influence of both ibuprofen and orthofen. These experiments showed that ibuprofen, unlike orthofen, also increases the resistance of the rat myocardium to hypoxia. For instance, the period before the beginning of bradycardia in response to anoxia was 2.5 times longer in animals receiving ibuprofen than in the control.

In the circulatory form of hypoxia ibuprofen and orthofen increased the number of surviving animals after occlusion of the common carotid arteries (Fig. 3).

Ibuprofen thus proved to be an effective antihypoxic agent on different models of hypoxic states in animals of different species, and when administered by different routes. Orthofen was less active, but this drug also gives an antihypoxic effect on models of asphyctic and circulatory hypoxia in rats. Meanwhile aspirin and butadione had no appreciable action.

The results are evidence that the antihypoxic action does not correlate completely with the ability of the various NSAIA to inhibit PG biosynthesis, for they are all to some degree inhibitors of the cyclo-oxygenase pathway of arachidonic acid metabolism. Ibuprofen, which

possesses stronger antihypoxic activity than orthofen, is a weaker inhibitor of PG biosynthesis than orthofen, whereas neither aspirin nor butadione exhibited any antihypoxic activity. However, we know that in some cases positive correlation does not exist between the activity of inhibitors of various enzymes in vitro and their action in vivo [7]. The view that the antihypoxic action of ibuprofen may be linked with inhibition of the arachidonic acid cascade (at least one of the possible mechanisms of its action) is supported by the protective action of ibuprofen against the lethal effect of sodium arachidonate in rabbits [4].

The results are evidence that the new NSAIA orthofen and ibuprofen, which are widely used at the present time, possess antihypoxic properties and that the study of the presence of these properties in other antiinflammatory agents influencing PG biosynthesis is indicated.

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DIPYROXIME AS A BLOCKER OF ACETYLCHOLINE-ACTIVATED IONIC CHANNELS IN RAT SKELETAL MUSCLE

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Dipyroxime (TMB-4) is a classical representative of the oximes, which are widely used in the treatment of poisoning by organophosphorus compounds which inhibit acetylcholinesterase (AChE) [1]. It has been suggested that the fundamental molecular mechanism of the antidotal action of the oximes is their ability to reactivate AChE, including skeletal muscular AChE [5]. At the same time, we know that the mechanism of the antitoxic action of these substances in vivo is much more complex and involves several components [1]. One such component is the cholinolytic action, which is manifested in skeletal muscles with both inhibited and intact AChE [4].

EXPERIMENTAL METHOD

Experiments were carried out in November on a rat phrenic nerve — diaphragm preparation with uninhibited AChE. The isolated muscle was placed in a bath with capacity of 1.5 ml, with continuously flowing Ringer–Krebs solution of the following composition (in mM): NaCl — 137, KCl — 5, $CaCl_2$ — 2, $MgCl_2$ — 1, $NaHCO_3$ — 11, NaH_2PO_4 — 1.0, glucose 11.0. The solution, which was aerated beforehand for 1 h with carbogen (95% oxygen, +5% carbon dioxide) had pH 7.3. The experiments were carried out at 21 ± 0.1°C. The membrane potential of the muscle fiber in the region of the synapse was clamped by a two-electrode method. The amplitude and temporal parameters of the miniature end-plate currents (MEPC) were analyzed by computer with 29 μsec signal quantization interval.

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