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EFFECT OF DALARGIN ON BRAIN TISSUE XANTHINE OXIDASE ACTIVITY DURING MYOPLEGIA

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KEY WORDS: brain; xanthine oxidase; dalargin; Arduan.

The hexapeptide dalargin, a Soviet analog of endogenous Leu-enkephalin, whose effects are realized by interaction with peripheral μ- and Δ-opiate receptors, in doses of up to 500 μg/kg does not in fact pass through the blood-brain barrier and does not act on central targets [3]. The possibility of using dalargin as a basic agent for anesthesiologic protection, as a component of multicomponent general analgesia has been investigated in the Department of Anesthesia and Resuscitation of the A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR [6-8]. The facts described above will serve as evidence of the importance of the study of the connection between the antinociceptive action of dalargin, when used in therapeutic doses, with another component of general anesthesia, namely myoplegia. The antioxidative effect of dalargin on the liver [5] and pancreas [2] has been demonstrated experimentally, and it has therefore been used for the prevention of postoperative pancreatitis.

The aim of this investigation was to study activity of an intracellular enzyme, xanthine oxidase (EC 1.2.3.2), catalyzing the formation of hydrogen peroxide and the superoxide anion-radical, one component of the lipid peroxidation (LPO) system, in the brain, which can serve as an important metabolic test of the efficacy of action of the opioid peptide analog dalargin.

EXPERIMENTAL METHOD

Experiments were carried out on 70 noninbred albino rats weighing on average 200 g, anesthetized with ether. Tracheotomy was performed on all the animals, and the trachea was intubated with a PVC catheter, which was followed by mechanical artificial ventilation of the lungs (AVL) under moderate hyperventilation conditions: respiration rate 70 cycles/min, volume 2.1-2.3 ml. To make the conditions of the model as close as possible to those in clinical medicine, all the preparations were injected into a central vein (the right jugular), into which 18 g/1.2 mm OD (Sweden) venous cannulas had been introduced. The animals were divided into four groups: groups 1 (control) consisted of 15 rats without myoplegia, receiving an injection of

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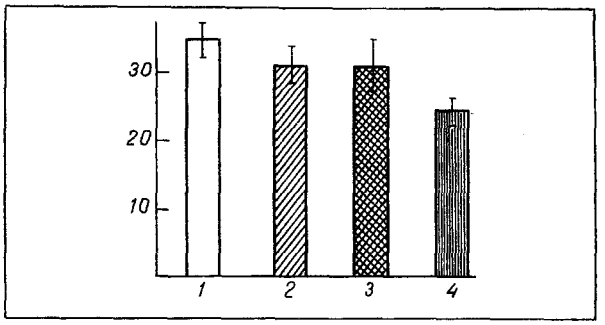

Fig. 1. Effect of dalargin on xanthine oxidase activity in brain tissue. Vertical axis, quantity of reduced ferricytochrome (in nmoles/mg protein); 1) 0.9% NaCl, 2) dalargin, 3) Arduan + 0.9% NaCl, 4) Arduan + dalargin.

physiological saline; group 2 consisted of 20 rats without myoplegia, receiving dalargin (40 μg/kg); group 3 consisted of 15 rats subjected to total myoplegia with Arduan ("Gedeon Richter," Hungary; 0.1 mg/kg) and receiving physiological saline; group 4 consisted of 20 rats receiving the same doses of the muscle relaxants and also dalargin (40 μg/kg). The opioid peptide was dissolved in physiological saline and injected intravenously in a volume of 0.1 ml; physiological saline was used as the placebo in the appropriate volume. Dalargin was synthesized in the Laboratory of Peptide Synthesis (Head, Professor M. I. Titov), All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR. Toward the end of the second minute after injection of the test preparation the animals were decapitated, the brain stem was quickly removed, and fixed in liquid nitrogen. Xanthine oxidase activity in the brain tissue was determined by the method in [10] and expressed in nanomoles of reduced ferricytochrome per milligram protein. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that when dalargin was injected into animals without myoplegia, no significant changes in brain xanthine oxidase activity were observed compared with the control. Against the background of total myoplegia, injection of physiological saline likewise was not accompanied by any significant changes in xanthine oxidase activity.

In the group of animals receiving dalargin during Arduan-induced myoplegia, injection of the opioid peptide caused a significant decrease in xanthine oxidase activity by 24.7% ($p < 0.01$), which in our investigation was a marker of the central action of dalargin. The relatively high level of xanthine oxidase activity in the control group compared with the remaining series can evidently be explained by the stressor action of the inhalation anesthetic which was used [9], and also by hypoxia and ischemia, associated with the general anesthesia and subsequent reoxygenation when AVL ceased to be applied [1].

In our opinion the very weak tendency toward a fall of enzyme activity in group 2 can be explained by minimal penetration of dalargin or its penta- and tetrapeptide fragments, which also possess opioid activity [4], into the CNS. In group 3, a similar fall can be attributed, not to the action of the placebo, but to the effect of the muscle relaxant administered previously, and which can be regarded as a nonpeptide ligand of opiate receptors.

Myoplegia induced by antidepolarizing relaxants and AVL thus create the real possibility for interaction between dalargin, a Leu-enkephalin analog, and central structures of the opioidergic system. The fact that dalargin possesses adequate antioxidative activity allows it to be recommended for use as a component in multicomponent general anesthesia.

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DISTRIBUTION OF A NEUROSPECIFIC CARDIOACTIVE PROTEIN–HORMONAL COMPLEX IN RATS WITH EXPERIMENTAL MYOCARDIAL ISCHEMIA

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Over a long period we have collected abundant factual evidence that cardioactive protein–hormonal complexes which we have identified in the magnocellular nuclei of the hypothalamus in man and various animals [2, 4, 6] are biochemical systems which are responsible for the chemical regulation of metabolism and of the functions of various visceral organs and, in particular, cardiovascular activity [8]. On dissociation of these complexes, the high-molecular-weight component has been shown to consist of new neurospecific glycoproteins, and the low-molecular-weight compounds noncovalently bound with them are cardiotrophic neurohormones, discovered previously in the same brain region and conventionally known as K, S, and G [3].

With the aid of highly specific antisera obtained to these protein–hormonal complexes and by methods of immunoelectrophoresis [[1] and radioimmunoassay (RIA), their specificity for nerve tissue has been proved, their subcellular localization studied, and their concentrations and distributions in the rat have been determined [6]. The use of RIA has opened up fundamentally new prospects for the study of the varied functions of neurospecific complexes involved in the hormonal regulation of cardiovascular activity by the CNS under normal and pathological conditions.

The aim of this investigation was to study brain levels and regional distribution of one of these complexes, namely protein-neurohormone K (PNK) in a model of experimental myocardial ischemia (MI) in rats.

EXPERIMENTAL METHOD

Experiments were carried out on 70 noninbred male albino rats weighing 160-200 g. Experimental MI was induced by ligation of the descending branch of the left coronary artery. Maximal development of MI on the 4th day was judged by recording the ECG on a 6NEK-3 apparatus (needle electrodes, unrestrained rats). The ECG of the animals was recorded in three standard leads, before and 5 min after occlusion of the coronary artery and before sacrifice of the animals. A few minutes more after occlusion of the left coronary artery the rats exhibited marked ischemic changes: a considerable rise of the ST segment and enlargement of the T wave on the ECG in standard leads. Later, three days after occlusion of the coronary artery, signs of established MI were observed on the ECG: as a rule a QS complex or a deep Q wave would be seen.

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