PHOSPHOLIPID METABOLISM IN THE BRAIN AND LIVER OF RATS POISONED WITH ORGANOPHOSPHORUS COMPOUNDS

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Organophosphorus compounds LG-63 and GA-81 did not affect the phospholipid content in the brain and liver tissue or the rate of renewal of phospholipids in the brain. However, compound LG-63 increased the intensity of phospholipid metabolism in the liver by 24.8% and GA-81 increased it by 32.4%.

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Since the action of organophosphorus compounds (OPC) on the body is not confined to their anticholinesterase effect [4], it is of considerable importance to examine the effect of these compounds on other aspects of metabolism.

The object of the present investigation was to study the effect of poisoning by a number of OPC on phospholipid (PL) metabolism in the brain and liver of rats. Data in the literature on this problem are conflicting [9-11].

For this investigation, compounds LG-63 and GA-81 were chosen as OPC. They differ in toxicity and in their ability to penetrate through the blood-brain barrier.* Compound LG-63 [$C_2H_5O(CH_3)P(O)SC_6H_{12}$] penetrates readily through the blood-brain barrier whereas GA-81 [$C_7H_{15}O(CH_3)P(O)SC_2H_4S(CH_3)C_2H_5$] penetrates hardly at all into the brain when injected intramuscularly and possesses much higher toxicity. The results of investigations undertaken at the Department of Biochemistry, First Leningrad Medical Institute [5], showed that compound LG-63 if injected intramuscularly in a sublethal dose inhibited the brain cholesterase by 90% after 2 h, whereas GA-81 under the same experimental conditions had no effect on the brain cholinesterase activity. When comparing the results of the action of these two compounds, information concerning the possible specific reaction of the PL metabolism of the brain to administration of different OPCs was also deliberately obtained. For this purpose, the effect of both OPCs on the intensity of PL metabolism not only in the brain, but also in the liver, was investigated in parallel experiments.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar albino rats weighing 200-240 g. The rats of group 1 received compound LG-63 intramuscularly (5 mg/kg), and the animals of group 2 received compound GA-81 (0.4 mg/kg) in the same way. OPC poisoning in the rats of group 1 was manifested by salivation, hemorrhagic lacrimation, and convulsions which were fibrillary in character and lasted throughout the experiment. OPC poisoning in the rats of group 2 was manifested by more severe salivation and lacrimation, but not by convulsions. Thirty minutes after injection of OPC, i.e., when well marked signs of poisoning were present, the animals of both groups (and also control rats 30 min after injection of physiological saline) received a subcutaneous injection of radioactive phosphate ($Na_2HP^{32}O_4$) in a dose of 0.5 μCi/g. The animals were sacrificed by decapitation 120 min after injection of the isotope. The brain and liver were removed, their membranes and vascular plexuses discarded, and blood thoroughly rinsed away with physiological saline. Lipids were extracted three times with 2:1 chloroform-methanol mixture by Folch's method. PL

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phosphorus was determined quantitatively after mineralization of the samples and radioactivity was measured on a T-25 BFL end-type counter. The rate of renewal of PL phosphorus was estimated from the relative specific radioactivity, the ratio between the specific radioactivity of PL phosphorus and the specific radioactivity of the inorganic phosphate of the brain and liver tissues.

EXPERIMENTAL RESULTS AND DISCUSSION

Poisoning with neither compound caused changes in the PL content in the brain and liver of the rats. The PL concentration in the brain (in μg phosphorus/g moist tissue) was 1965±52 for the normal rats, 1990±28 for the rats of group 1, and 2011±45 for the rats of group 2. The corresponding values for the liver were 1397±31, 1408±21, and 1444±33 μg phosphorus/g tissue. The absence of changes in PL concentration in the investigated tissues in OPC poisoning confirms the high resistance of the phospholipid composition of the tissues to pathogenic agents [6, 7]. Poisoning of the rats by either of the OPCs used likewise did not cause any changes in the relative specific radioactivity of the PL in the brain tissue. In the liver, however, an increase in the relative specific radioactivity of the PL was found (10.7±0.5 for normal rats, 13.3±1.1 for rats of group 1, and 14.1±0.8 for rats of group 2; P 0.05 and 0.001 respectively).

In rats poisoned with LG-63 the rectal temperature fell by 2.7°, while in rats poisoned with GA-81 it was unchanged.

The results show that neither the cholinesterase inhibitor penetrating (LG-63) nor that not penetrating (GA-81) through the blood-brain barrier produced any changes in the intensity of PL metabolism in the rat brain. This result was rather unexpected in the experiments with LG-63, which produced a marked fall of rectal temperature, itself leading to a decrease in the rate of PL metabolism [1, 3]. The fall in body temperature observed in the rats of group 1 could be the result of anoxia arising during OPC poisoning, although the direct action of the inhibitor on the thermoregulatory center cannot be ruled out [4]. The absence of lowering of PL metabolism in the brain of the rats of group 1 suggests that during OPC poisoning hypothermia is not the only factor influencing PL metabolism in the brain. Convulsions of different origin are known to increase the rate of PL metabolism in the brain [2], and it may thus be considered that the absence of changes in PL metabolism in the brain of the rats of group 1 was the result of opposite effects of these two factors accompanying poisoning—hypothermia and convulsions.

One possible explanation of the increase in PL metabolism in the liver under the influence of OPC is given by the results of investigations of Hokin and co-workers [8], who demonstrated that PL metabolism can be stimulated in some secretory organs by the action of acetylcholine and acetylcholinesterase compounds. It may also be postulated that the increase in the intensity of PL metabolism in the liver observed under our experimental conditions reflects to some degree the increase in function of the liver cells associated with detoxication of the cholinesterase inhibitors.

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