prevented by the fact that the transhemation reaction is species specific for man, i.e., the plasma proteins of other mammals and, in particular, of laboratory animals such as dogs, rabbits, rats, cats, and guinea pigs, do not take part in it [2, 8].

Consequently, the transhemation reaction to HSA must play an important role in metabolism of an artificial oxygen carrier based on Hb.

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PREVENTION OF POSTISCHEMIC DISTURBANCES BY NEW ADENOSINE DERIVATIVES

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The study of methods of prevention and treatment of postischemic disorders has a relatively short history. Different approaches to the solution of this problem have been discussed [1, 2, 7], in particular: 1) the possibility of using artificial electron carriers, capable of relieving the load on the respiratory chain and of restoring oxidative phosphorylation; 2) the use of antioxidants, limiting the oxygen consumption mainly by inhibiting free (nonphosphorylating) oxidation and limiting the accumulation of lipid peroxidation (LPO) products; 3) the use of antifatigue agents, accelerating recovery processes, due both to their effect on mechanisms of protein synthesis and to the increased efficiency of tissue respiration, ATP production, and the more rapid utilization of products of anaerobic metabolism; 4) future prospects for a new class of antihypoxic agents based on adenosine. Stable adenosine analogs, namely allyladenosine (ALAD) and cyclohexyladenosine (CHAD), which are purine receptor agonists, have a marked antihypoxic and protective action in cerebral ischemia [8].

The aim of this investigation was to estimate the efficacy of these compounds as agents preventing postischemic disturbances associated with liver damage induced by ischemia.

EXPERIMENTAL METHOD

Experiments were carried out on 120 male albino rats weighing 180-200 g. The experimental model was acute hypoxia of the liver, induced by compressing the hepatoduodenal ligament (HDL). Under ether anesthesia the liver was

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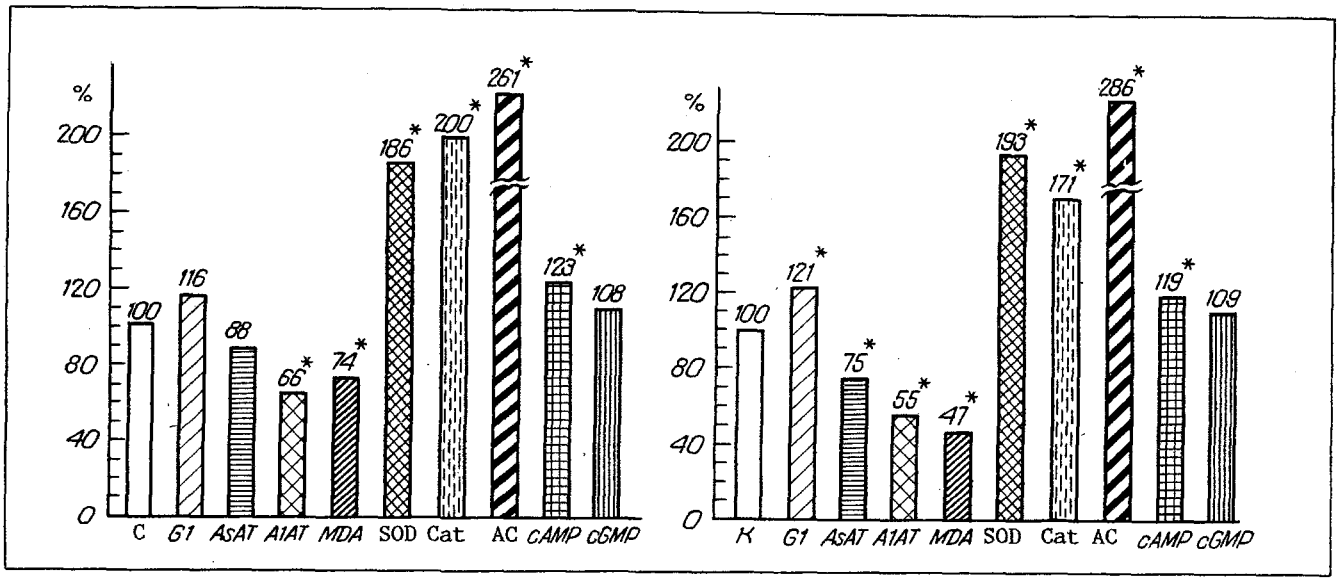

Fig. 1 Fig. 2

Fig. 1. Efficacy of protective action of ALAD on model of circulatory hypoxia of the liver. Abscissa: C) control; Gl) glucose concentration; AsAT) aspartate aminotransferase; AlAT) alanine aminotransferase; MDA) malonic dialdehyde; Cat) catalase; AC) antioxidase coefficient; cAMP) cyclic 3,5-adenosine monophosphate; cGMP) cyclic 3,5-guanosine monophosphate; Ordinate, levels of test substances (in of control).

Fig. 2. Efficacy of protective action of CHAD on model of circulatory hypoxia of the liver. *$p < 0.05$ compared with control group. Remainder of legend as to Fig. 1.

exposed through a midline laparotomy incision, a clip was applied to HDL, after which, to prevent hypothermia, the rats were placed for 20 min in a heated cupboard in which the air temperature was 37°C. The animals were decapitated 24 h after removal of the clip and surgical treatment of the wound. Blood was collected in test tubes; the liver was washed in cold physiological saline and frozen in liquid nitrogen. Enzyme (AlAT and AsAT) activity and total protein and glucose concentrations were measured on a "Technicon" biochemical analyzer. The malonic dialdehyde (MDA) concentration in the liver tissue was determined by the method in [5] and activity of the enzymes superoxide dismutase (SOD) and catalase (Cat) by the methods in [3, 6]. The cyclic nucleotide (cAMP and cGMP) levels in the liver were determined by radioimmunoassay, using test systems from "Amersham" (England). Adenosine analogs (synthesized at the All-Union Research Institute for Technology of Antibiotics and Enzymes of Medical Importance), namely ALAD and CHAD, were injected intraperitoneally in a single dose of 0.1 and 0.01 mg/kg, immediately after removal of the clip from HDL.

EXPERIMENTAL RESULTS

The experiments showed that the postischemic period is accompanied by marked injury to the hepatocytes, as may be judged from the sharp increase in the serum AsAT and AlAT levels. This increase in transferase activity points to injury to both cell and mitochondrial membranes. During reperfusion activation of LPO was observed: the content of MDA, a secondary product of LPO, increased whereas activity of enzymes of the antioxidase systems (SOD and Cat) decreased. The fall of the glucose level during reperfusion indicates inhibition of the glucose-synthesizing function of the liver. Damage to hepatocyte membranes may be responsible for loss of cyclic nucleotides by the cells and for lowering of their concentration, which was observed in the experiments. Meanwhile the possibility cannot be ruled out that this fall takes place as a result of reduction of the ATP reserves in the liver during reperfusion.

The adenosine analogs ALAD and CHAD had a marked protective action on the liver in the postischemic period. For instance, the normal serum transaminase levels were restored, evidence of restoration of the integrity of the cell membranes. The MDA level, characterizing LPO in the liver (Figs. 1 and 2) became stabilized. Synthesis of SOD and Cat, which is especially important during reoxygenation, was restored. Products of adenosine metabolism are substrates for the

xanthine oxidase reaction, which stimulates LPO. However, earlier experiments showed that ALAD and CHAD not only do not undergo deamination in the presence of adenosine deaminase, can themselves inhibit adenosine deaminase [4].

The considerable rise of the cAMP level in the hepatocytes which, in our opinion, may be one possible explanation of the protective effect of the analogs tested, is particularly interesting. It can be postulated that during reperfusion, when normal functioning of the cell membrane is disturbed and the receptor sites are less able to bind with primary messengers, ALAD and CHAD (through activation of A_1-adenosine receptors) induce resensitization of the receptors which, in turn, leads to a rise of the cAMP level followed by normalization of intracellular metabolism. We showed previously that these adenosine analogs bind chiefly with A_1-adenosine receptors of the guinea pig ileum [8].

We know that cAMP has a marked stimulating action on hepatocyte proliferation and regeneration of the liver, by stimulating RNA [11] and DNA [10, 12] synthesis. Incidentally, we determined cAMP and cGMP 24 h after ischemia, when the intensity of regeneration in the liver after injury is maximal [9], and the adenosine analogs maintained their activity for several hours. Activation of cAMP synthesis by ALAD and CHAD, and the associated stimulation of regenerative processes in the liver can evidently explain the normalization of parameters reflecting liver damage in the postischemic period.

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