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LIPID METABOLISM IN EXPERIMENTAL VIRUS INFECTIONS

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Despite much progress in the study of the nature of virus infections in recent years their pathogenetic aspects have by no means been fully investigated. This is truest of all for metabolic disturbances, which may accompany virus diseases. Yet a comprehensive study of the role of viruses in disturbances of normal homeostasis at the whole body level is important not only from the standpoint of a fuller understanding of the pathogenesis of virus infections themselves, but also in order to establish the importance of particular viruses in what have been called metabolic somatic diseases, whose etiology and pathogenesis remain incompletely explained. One such disease is atherosclerosis, in respect of which an association with viruses has been established [4, 11, 12, 13].

The aim of this investigation was an experimental study of the effect of herpes simplex and influenza viruses on lipid metabolism. The blood serum lipid spectrum of the animals and the content of free lipids in cells of the aorta were studied in model experiments in vivo and in vitro. The choice of virus models was determined by the following factors: the wide distribution and massive prevalence of herpetic and influenzal infections caused by viruses, and the depth and severity of the damage caused to individual organs and systems in these diseases [3, 8].

EXPERIMENTAL METHOD

A model of herpetic infection, namely keratoconjunctivitis (HKC) was created in chinchilla rabbits weighing 2-2.5 kg, with the aid of type 1 herpes simplex virus (HSV1, Koptev strain), with an infecting dose (ID) of 100 LD_{50} [5]. A model of influenzal infection (II) was created in noninbred albino mice (weighing 15-20 g), using influenza virus (IV, strain A/Aichi/2/68 [H3N2]), with IV of 0.35 LD_{50} [2]. As inhibitor of KC we used Furavir, a guanine derivative (synthesized at the Institute of Organic Synthesis, Latvian Academy of Sciences), with combined administration in the form of intravenous injections (20 mg/kg daily for 8 days) together five repeated instillations of a 3% solution. As inhibitor of II we used remantadine (produced by the "Latbiofarm" Combine) in a dose of 12.5 mg/kg, given by the intragastric route 1 h before infection, and then three times, 24, 48, and 72 h respectively after infection. Each experimental group consisted of 6 animals. Concentrations of triglycerides (TG) were determined by the method in [15], total cholesterol (Chs) by Ilka's method [15], α-Chs by the same method after precipitation of β-lipo-

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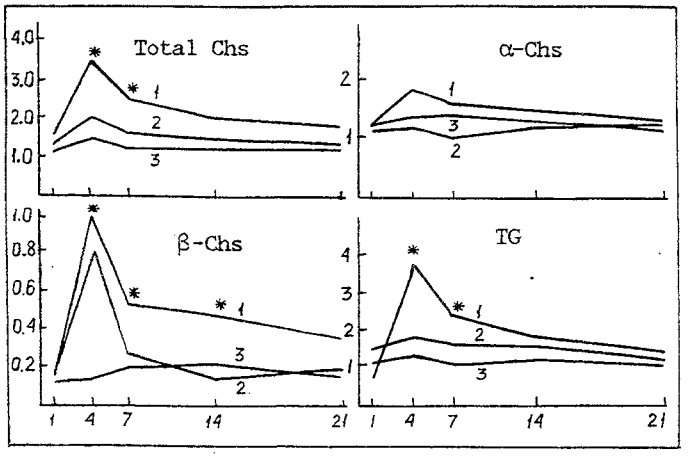

Fig. 1. Blood lipid serum spectrum of rabbits with HSV infection and treated with Furavir. 1) Infected rabbits control; 2) Rabbits with KC, treated with Furavir; 3) Control healthy rabbit (intact, not infected). $^*p_{1-3} < 0.01$.

proteins by heparin in the presence of manganese salts [10]. The β-Chs level was determined by finding the difference between total Chs and α-Chs. The results were subjected to statistical analysis [9]. Experiments to study levels of free intracellular lipids in the presence of experimental herpetic (strain 1 "C," 0.01-0.001 PFU/cell) and influenzal (strain A/FPV/Rostock [H7N1], 0.01-0.001 PFU/cell) infections were carried out on a culture of human embryonic aortic cells (HEA). At the 18th hour of infection, cells grown on coverslips were fixed and stained with Sudan Black B [6]. The concentration of free intracellular lipids was compared by determining the color density on an "Integrall" instrument ("Kvant," Kiev) [1].

EXPERIMENTAL RESULTS

The model of GC was characterized by typical clinical features [5], which were manifested most intensively on the 4th-5th day after infection. Clinical recovery when Furavir was used took place by the middle of the second week. The infection was accompanied by marked viremia. The virus was isolated also from the liver and brain and on the 14th day of infection its titer was >3.5 and >5.5 log LD_{50} respectively.

A comparative study of the lipid spectrum of the blood serum of intact rabbits and rabbits infected with HSV over a period of time revealed significant differences in concentrations of total Chs, β-Chs, and TG. These differences, toward an increase, were particularly marked at the peak of infection (4th-7th days). The α-Chs level in the infected animals did not change significantly: no significant differences were found at any times of observation in the groups of infected and intact animals. On the 21st day lipid concentrations were similar to those recorded at the beginning of infection, although they did not return completely to normal (Fig. 1). The time course of the serum lipid levels of the infected animals correlated with that of viremia and the clinical manifestations of KC. The use of Furavir in a therapeutic dose led to correction of the lipid spectrum of the rabbits with KC (Fig. 1).

The model of influenzal infection in the mice followed the classical course [3]. The presence of production infection was confirmed by isolation of the virus from the lungs on the 1st, 4th, and 8th days after infection. The titer of isolated virus was 2.75, 5.03, and 3.36 log LD_{50}/0.05 ml respectively when titrated in mice and 4.16 and 16 hemagglutination units (HAU)/ml respectively when the virus was isolated in chick embryos and titrated in the hemagglutination test. A study of the blood serum lipid spectrum showed that concentrations of total Chs, α-Chs, β-Chs, and TG in the infected animals did not differ from that in intact rabbits (Fig. 2).

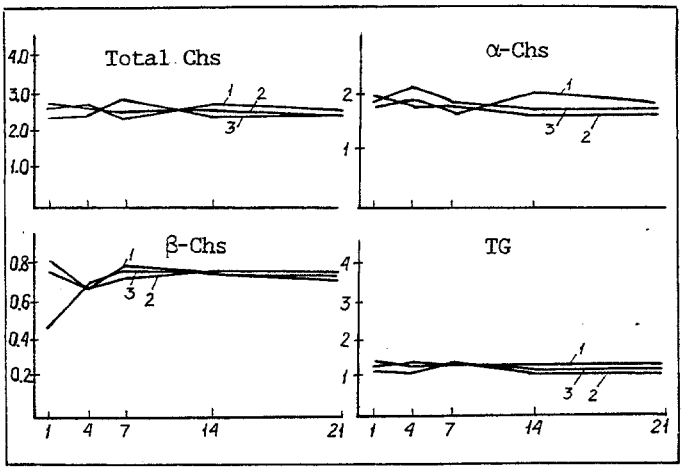

Fig. 2. Blood lipid serum spectrum of mice with IV infection and treated with remantadine: 1) Infected mice control; 2) Infected mice treated with remantadine; 3) Healthy mice control (intact, not infected).

The results of a comparative study of the ability of HSV and IV to affect lipid accumulation by a culture of HEA cells were as follows. Infection of the culture with HSV was accompanied by a significant increase in the intracellular lipid concentrations, as shown by the color density of the cytoplasm of the infected cells, stained for lipids, compared with that of intact cells (34.7 ± 1.6 and 20.21 ± 0.6 respectively). Infection of the culture under these experimental conditions with IV had virtually no effect on levels of free intracellular lipids: no significant differences were observed between the color density levels of the stained lipids in intact and infected cells (20.21 ± 0.6 and 16.03 ± 0.9 respectively). Thus, of the two viruses which we studied in systems in vivo and in vitro. Only HSV was able to affect lipid metabolism. This virus, unlike IV, induced dyslipidemia in the rabbits and increased accumulation of free lipids by aortic cells in culture.

On the basis of these results a number of hypotheses can be put forward with respect to prospects for future research in this direction. It is event that if these viral agents are studied relative to their "lipid-modulating" properties, considerable scatter of the results is to be expected. It is logical to suppose that, depending on the structure, biological properties, and affinity for particular organs, different viruses can differ greatly in their effect on lipid metabolism, or they may not alter it at all. It can also be tentatively suggested that mainly infections accompanied by damage to organs and systems involved in catabolism and/or anabolism of lipids will be accompanied by lipid disturbances. This view is supported by data showing profound changes in lipid metabolism in patients with virus hepatitis [7]. HSV infection under conditions of generalization can, as we know, be accompanied by the development of herpetic hepatitis. From this standpoint, our results, obtained on a model of herpetic infection, appear perfectly logical especially if the fact that highly infectious virus was isolated from the liver of the experimental animals is taken into consideration.

The results of the present investigation, by deepening our existing views on the pathogenesis of herpetic and influenzal infections, may prove useful in defining the role of the viral factor in the etiology and pathogenesis of physical diseases accompanied by the disturbances of lipid homeostasis.

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