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IMMUNOMEDIATED INDUCTION OF HYPERLIPOPROTEINEMIA

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The concept of metabolic immunodepression postulates that immunity is dependent on lipid and carbohydrate metabolism [2]. The mechanism of this dependence is determined by the immunoregulatory properties of lipoproteins: the inhibitory action of low-density and very low-density lipoproteins (LDL and VLDL, respectively) on immunocompetent cell function [5]. It has also been observed that immunization and virus infections lead to hyperlipidemia, which is transient and is independent of the fat content in the diet and the nature of the sensitizing agent [3, 9-11].

The aim of this investigation was to study dependence of immunocompetence of the body on hyperlipidemia and, second, dependence of lipid and lipoprotein metabolism on the state of the immune system during both immunodepression and immunostimulation.

EXPERIMENTAL METHOD

Hyperlipidemia was induced experimentally in male C57BL/6 mice. Control mice were kept on an ordinary diet whereas the experimental animals were given egg yolk ad libitum. The blood sera of the mice were tested on the 10th day after the beginning of the experiment. At the same time lipophoid cells isolated from the mouse spleen were investigated. The well-known model of virus-induced Rauscher leukemia [1] was used as the model of acquired immunodeficiency. To study the lipid profile during antigenic stimulation, experimental models of the formation of an immunocomplex lesion of the glomeruli in mice in situ by preliminary sensitization, and also in the presence of a raised level of circulating immune complexes

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TABLE 1. Immunobiochemical Parameters of C57BL/6 Mice on 10th Day of High-Cholesterol Diet (M ± m)

Parameters	Control	Experiment
Cholesterol, g/liter, total	0,84±0,03	1,24±0,06*
nonesterified	0,25±0,01	0,42±0,03*
VLDL + LDL, %	41,1±1,45	87,9±1,39*
HDL, %	58,9±1,45	12,1±1,39*
CIC, g/liter	1,36±0,02	2,81±0,09*
AFC per 10^6 cells	52,7±2,59	24,0±3,35*
AITL with PHA, %	27.8±2,23	9,5±,091*
AITL with con.A, %	23,5±1,46	6,6±0,80*
AITL with LPS, %	37,0±1,88	10,0±1,24*

Legend. PHA) Phytohemagglutinin; con A) concanavalin A; LPS) lipopolysaccharide.*p < 0.001 compared with control.

TABLE 2. Immunobiochemical Parameters of BALB/c Mice in Leukemia-Associated Immunodeficiency and during Immunostimulation of Immunocomplex Pathology (M ± m)

Parameters	Control	Rauscher leukemia	Complex formation in situ	Passive injection of complexes
Cholesterol, g/liter, total	0,97±0,03	1,18±0,03*	1,18±0,04*	1,04±0,05
nonesterified	0,26±0,01	0,13±0,01*	0,32±0,02**	0,29±0,01
VLDL + LDL, %	32,0±2,15	22,3±2,80***	42,2±2,18**	34,8±1,58
HDL, %	67,7±2,04	77,7±2,80***	57,8±2,18**	65,1±1,58
CIC, g/liter	0,64±0,04	2,04±0,04*	1,66±0,07*	2,04±0,05*

Legend. *p < 0.001, **p < 0.01, ***p < 0.02, ****p < 0.05 compared with control.

(CIC) in the blood following passive injection of preformed immune complexes [6], were used. Altogether six series of experiments were carried out on BALB/c mice. Parallel tests were carried out on four groups of animals: 1) control mice; 2) mice with leukemia; 3) mice with immunocomplex pathology in situ; 4) mice with passive injected immune complexes.

Rauscher leukemia was induced by inoculation of BALB/c mice with plasma virus, and the blood sera were subsequently investigated on the 21st day, when clinically developed leukemia was present. To form immunocomplex pathology in situ the mice were given an intravenous injection of 0.1 ml of human serum albumin (HSA), followed 6 h later by rabbit antibodies to HSA (Behringwerke, West Germany), also intravenously, in a dose of 0.1 ml. Immune complexes preformed in vitro were obtained by incubation of equal volumes of HSA (1 mg/ml) and antibodies to HSA in a dilution of 1:1 for 1 h at 37°C. The test parameters were determined in the blood sera 72 h later. The concentrations of total and free (nonesterified) cholesterol were determined in the blood sera and the lipoproteins were fractionated by electrophoresis in agarose gel. The CIC concentration was determined by the method in [4]. Lymphocyte function was determined by the adhesion inhibition test on leukocytes (AITL) stimulated by mitogens [7]. The number of antibody-forming cells (AFC) in a suspension of mouse spleen cells was determined by the method in [8]. The results were subjected to statistical analysis on the Hewlett-Packard HP 9815A computer.

EXPERIMENTAL RESULTS

Alimentary hyperlipoproteinemia (HLP) in C57BL/6 mice was accompanied by characteristic redistribution of the lipoproteins: elevation of LDL and VLDL levels accompanied by a marked fall in the level of high-density lipoproteins (HDL). The blood levels of total and nonesterified cholesterol and also of CIC were significantly raised (Table 1). Meanwhile functional activity of the splenic lymphocytes of the mice against this background was strongly depressed, as was shown by a decrease in the number of AFC and in the degree of inhibition of adhesion of mitogen-stimulated cells. Consequently, HLP induces a state of marked immunodeficiency with depressed function of immunocompetent cells against the background of a high CIC level.

Dependence of lipid and lipoprotein metabolism on the state of immunoreactivity of the animal was clearly demonstrated in BALB/c mice exposed to immunomodulating influences. Electrophoresis of lipoproteins revealed the opposite redistribution of lipids among lipoprotein classes in immunodeficient mice with Rauscher leukemia and in immunostimulated mice during immune complex formation in situ (Table 2). An increase in the percentage content of HDL was observed in carcinogenic immunodeficiency, and conversely, the LDL + VLDL level was raised during antigenic stimulation. Against the background of this redistribution significant changes were found on analysis of nonesterified cholesterol, the concentration of which fell considerably in the blood of leukemic mice and was increased significantly in mice with immunocomplex pathology; the total cholesterol level was raised equally in both sets of mice.

In mice with passively injected immune complexes performed in vitro, the CIC concentration was significantly higher than in mice with immune complexes formed in situ ($p < 0.001$).

However, under these circumstances no effect of a high CIC level on the character of lipid metabolism could be found. Consequently, disturbances of lipid metabolism depend, not on the CIC level, but on antigenic stimulation, acting on all components of the immune system. The high HDL level coupled with a low nonesterified cholesterol concentration in leukemic mice is evidence of considerable acceptance of cholesterol, which is evidently essential for the maintenance of progressive reproduction of tumor cells.

It can thus be concluded that antigenic stimulation is accompanied by the development of HLP with raised levels of cholesterol, LDL, and VLDL, which possesses immunoregulatory properties. Consequently, disturbance of immune homeostasis during antigenic stimulation and activation of the B system of immunity predetermines metabolic limitation of the humoral immune response, mediated by the immunoinhibitory properties of lipoproteins. HLP can thus be regarded as a compensatory, metabolic reaction of the organism, aimed at restoring immune homeostasis under conditions of antigenic stimulation and polyclonal activation of the B-system of immunity.

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