CAUSES OF INTENSIFICATION OF LIPID PEROXIDATION IN THE BLOOD SERUM OF PATIENTS WITH VIRAL HEPATITIS B

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A central place in the pathogenesis of viral hepatitis B is occupied by the cytolysis syndrome, characterized by increased permeability of hepatocyte cell membranes [9] and an increase in the concentrations of cytoplasmic enzymes and bilirubin in the blood serum [2]. Increased permeability of the cell membranes is associated with intensification of lipid peroxidation (LPO) [4]. Meanwhile, the causes of activation of LPO in hepatitis B are not quite clear. One such cause may be hypoxia [4], whose role in the pathogenesis of hepatitis B is generally familiar [1]. However, the serum LPO level depends on the state of the antioxidative system (AOS) of the blood. The principal components of the AOS of blood serum are cerulo-plasmin (Cp), transferrin (Tf) [11], and α-tocopherol [13].

We studied the causes of accumulation of LPO products in the blood serum of patients with hepatitis B.

EXPERIMENTAL METHOD

The following parameters were determined in the blood serum of 40 patients with hepatitis B (moderately severe in 34, severe in six patients) aged from 18 to 40 years, at the height of the illness. The level of hypoxia was estimated from the oxygen tension in the tissues [7] and lactate dehydrogenase (LDH) activity in the blood serum [5, 10]. To determine the oxygen tension in the tissues, the partial O_2 pressure in the deltoid muscle was measured with an open platinum electrode on an Lp-72 polarograph. LDH activity was determined on a "Kone-3000" clinical analyzer, using reagents from the firm "Kone," Finland). The intensity of LPO was estimated from the malonic dialdehyde (MDA) concentration, which was measured spectrophotometrically by the method in [12]. The α-tocopherol concentration was determined fluorometrically by the method in [14]. Serum levels of Cp and Tf were estimated by the electron paramagnetic resonance (EPR) method. The conditions of recording the EPR spectra were the same as in [8]. The antioxidative activity (AOA) of the blood serum was judged from the ratio between the EPR signals for Cp and Tf (Cp/Tf), as suggested in [8]. The degree of tissue destruction was estimated from the serum concentration of cytoplasmic enzymes (alanine transaminase – ALT).

The state of the liver function was assessed by the usual clinical biochemical tests.

The diagnosis of hepatitis B was based on clinical, epidemiologic, and laboratory data. The severity of the disease was determined by the use of generally accepted clinical and clinical-biochemical indicators. The control group consisted of 26 clinically healthy individuals of the same age.

EXPERIMENTAL RESULTS

The results indicate the presence of marked hypoxia in the patients with hepatitis B. The partial oxygen pressure in the tissues (p_tO_2) was lowered by half compared with the control in patients with moderately severe hepatitis B, and by two-thirds in patients with severe hepatitis B (Table 1). Meanwhile, the serum LDH concentration was increased sixfold in moderately severe and sevenfold in severe hepatitis B.

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TABLE 1. Partial Oxygen Pressure in Tissues and Some Parameters of the Blood Serum in Patients with Hepatitis B ($M \pm m$)

Parameter	Control	Moderately severe hepatitis B	Severe hepatitis B
p_tO_2, mm Hg	31±1,3	15±0,28**	11,0±0,4**
ALT, μM	0,22±0,01	1,33±0,05*	1,57±0,03*
LDH, μM	0,15±0,04	0,85±0,01*	1,11±0,01*
MDA, μM	0,048±0,001	0,161±0,004*	0,210±0,005*
Cp, conventional units	2,0±0,1	2,8±0,2	3,3±0,4***
AOA (Cp/Tf), conventional units	0,71±0,05	0,61±0,02	0,41±0,07**
α-Tocopherol	34,5±0,2	39,3±3,1	31,5±2,7
Bilirubin, μM	21±2	173±11*	243±5*

Legend. $*p < 0.001$, $**p < 0.01$, $***p < 0.05$ Compared with control.

Meanwhile, the MDA concentration in the blood serum was raised, evidence of intensification of LPO. The coefficient of correlation between MDA and LDH and also between MDA and p_tO_2 was +0.75 and +0.79, respectively, evidence of high correlation between the LPO levels and the degree of tissue hypoxia, which was evidently one cause of LPO activation in the tissues in hepatitis B.

In addition, the serum ALT concentration was increased (Table 1): this enzyme characterizes the intensity of the cytolytic effect in the liver during hepatitis B. The coefficient of correlation between the ALD and MDA concentrations was +0.75, suggesting that most MDA enters the blood serum from liver tissue. A study of the parameters of the AOS showed that the α-tocopherol concentration did not differ significantly in the two groups of patients. The Cp concentration was increased in accordance with the severity of the course of hepatitis B. This may reflect a compensatory reaction of the body in response to the intensification of LPO. Meanwhile, the serum AOA was depressed in hepatitis B patients by a degree which was directly related to the severity of the disease. This was due to an increase in the Tf concentration, bound with iron in the blood serum, reducing its AOA [8, 11]. It can be tentatively suggested that the fall of the total AOA is one cause (besides hypoxia) of the elevation of the serum level of LPO products in hepatitis B.

The bilirubin concentration rose depending on the severity of the disease. It is important to note that changes in the bilirubin concentration and AOA were opposite in direction. Bilirubin possesses antioxidative properties [3]. It can be postulated that in the presence of low AOA the bilirubin partly compensates this function of the serum AOS. At the same time the possibility of a toxic action of bilirubin cannot be ruled out, giving rise to a number of toxic manifestations and depressing the level of liver function [6].

The results as a whole thus suggest that the increase in the serum MDA concentration is associated, on the one hand, with its release from the tissues, notably the liver, which could be the result of hypoxia, and on the other hand, it may be linked with depression of the serum AOA.

LITERATURE CITED

1. V. P. Bezuglyi, Progress in Hepatology [in Russian], No. 3, Riga (1971), pp. 110-128.
2. A. F. Blyuger, Practical Hepatology [in Russian], Riga (1984).
3. A. F. Blyuger, L. B. Dudnik, A. Ya. Maiore, and L. E. Mieze, Byull. Éksp. Biol. Med., **99**, No. 2, 116 (1985).
4. Yu. A. Vladimirov and A. I. Archakov, Lipid Peroxidation in Biological Membranes [in Russian], Moscow (1972).
5. M. A. Dombrinskaya, Vopr. Med. Khim., **9**, No. 3, 279 (1973).
6. A. Ya. Ivanov and P. A. Susla, Klin. Med., **53**, No. 10, 86 (1973).
7. E. A. Kovalenko, V. A. Berezovskii, and I. M. Épshtein, Polarographic Determination of the Oxygen Tension in the Body [in Russian], Moscow (1975).
8. A. V. Kozlov, V. I. Sergienko, Yu. A. Vladimirov, and O. A. Azizova, Byull. Éksp. Biol. Med., **94**, No. 12, 668 (1984).
9. N. I. Nisevich, V. F. Uchaikin, and T. P. Moleva, Pediatriya, No. 6, 44 (1978).

10. I. Bartel, J. Diceknoff, S. Iwanoff, and R. Koch, Dtsch. Z. Gesund.-Wes., **52**, 2297 (1965).
11. J. Gutteridge, R. Richmond, and B. Halliwell, FEBS Lett., **112**, No. 2, 269 (1980).
12. M. Minara, M. Uchiyama, and K. Fukuzama, Biochem. Med., **23**, 302 (1980).
13. A. L. Tappel, Ann. New York Acad. Sci., **203**, 12 (1972).
14. S. L. Taylor, M. P. Lamden, and A. L. Tappel, Lipids, **11**, No. 7, 530 (1976).