Dynamic Blood Viscosity and Hepatic Microcirculation in Alloxan-Induced Diabetes Combined with Toxic Hepatitis

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Dynamic viscosity of blood and hepatic microcirculation were evaluated in two groups of male rats: rats with alloxan-induced diabetes mellitus to which acute toxic hepatitis was added by injection of the alkaloid heliotrine (group 1) and those with heliotrine-induced hepatitis to which diabetes was added by alloxan injection (group 2). While blood viscosity and hepatic microcirculation were altered in both groups (particularly on day 3 after hepatitis induction in group 1 and on day 14 after diabetes induction in group 2), the alterations were more strongly marked in group 1. The results of this study are interpreted as indicating an early decompensation of the mechanisms of adaptation (autoregulation) in the presence of these two diseases, especially when hepatitis is superimposed on diabetes.

Key Words: *diabetes, acute hepatitis; blood viscosity; hepatic microcirculation*

Hemorheological disorders and the associated functional/metabolic and structural alterations occurring in the liver in a number of pathological conditions have aroused increased interest in recent years [1,6] in view of the many vitally important functions performed by the liver and of the special burden it has to bear as a central organ of homeostasis in any disease. Particular interest is shown in the mechanisms by which homeostatic equilibrium is upset in combined diseases because, given the steadily increasing longevity in many countries and the declining case fatality rates, such diseases have become a public health problem of growing importance.

The aim of this study was to assess the rheological status of blood by measuring its dynamic viscosity and recording microcirculatory disturbances in the liver in diabetes mellitus combining with toxic hepatitis.

MATERIALS AND METHODS

The study was conducted on a total of 87 randombred male rats (initial body weight 150-230 g) divided into three groups. The first test group consisted of rats made diabetic by an intraperitoneal injection of alloxan hydrate (Chemapol) in a dose of 0.07 mg/g body weight and then given a single subcutaneous injection of the alkaloid heliotrine in a dose of 0.15 mg/g to produce acute toxic hepatitis. The second test group comprised rats in which, conversely, acute toxic hepatitis was first induced by heliotrine and diabetes mellitus was then added as just described. The third (control) group consisted of intact rats. Measurements of dynamic blood viscosity and hepatic microcirculation were performed on days 1, 3, 7, and 10 after the induction of hepatitis in the presence of diabetes (group 1) and on days 7 and 14 after the induction of diabetes in the presence of hepatitis (group 2). Dynamic viscosity was measured with an improved Udovichenko's method [4] at pressures of 2 to 16 mm H_2O applied to the blood flow. Hepatic microcirculation was evaluated on the indicated days by intravital biomicroscopy using a television system we had developed, in collaboration with the Institute of Television (St. Petersburg), for digital analysis of microcirculatory parameters [2].

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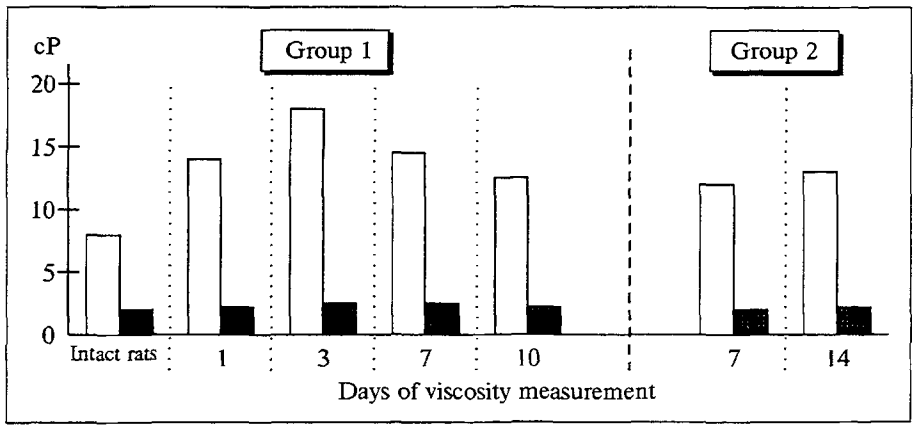

Fig. 1. Temporal variations of blood viscosity in rats of the two test groups. Shown are viscosity values in the areas of low (2 mm H_2O — white bars) and high (16 mm H_2O — black bars) pressures applied to the blood flow. Group 1: rats with hepatitis superimposed on diabetes; group 2: rats with diabetes superimposed on hepatitis.

RESULTS

Blood viscosity measurements in the three groups are summarized in Fig. 1. In the control (intact) group, viscosity values at the lowest (2 mm H_2O) and highest (16 mm H_2O) applied pressures were 8.53±0.06 and 1.45±0.09 cP, respectively. In group 1, as compared to the intact group, blood viscosity on day 1 was 61.8% higher at 2 mm H_2O and 22.1% higher at 16 mm H_2O, reached its peak value on day 3 (18.30± 0.69 cP at 2 H_2O and 2.33±0.13 cP at 16 mm H_2O), and tended to return toward normal subsequently (days 7 and 10), but was above the control values in all rats.

In group 2, as in group 1, increases in blood viscosity in the area of low applied pressures were greater than in that of high pressures, both on day 7 and on day 14. Blood viscosity values on day 14 were higher than on day 7, the mean values being 13.35±0.71 cP at 2 mm H_2O and 2.14±0.07 cP at 16 mm H_2O.

In group 1, the hepatic microcirculatory bed (MCB) appeared altered already on day 1 and presented on that and subsequent days a mosaic architectonic pattern, marked by an alternation of functional and nonfunctional sinusoids (mainly at the lobular periphery), areas of stasis with dilated (barrel-shaped) sinusoids, and functional microvessels that had increased diameters and walls with rather indistinct contours and impaired permeability. Blood flow rates were decreased throughout the hepatic MCB, being equal to 0.180±0.21, 0.158± 0.04, 0.145±0.13, and 0.110±0.08 mm/sec on days 1, 3, 7, and 10, respectively, *vs.* 0.261±0.036 mm/sec in the control group, despite the above-mentioned tendency toward normalization of blood viscosity on days 7 and 10. Additional tests showed further decreases in blood flow rates later, which may be interpreted as an indication that the mechanisms underlying the autoregulation of tissue blood flow were impaired.

Similar changes in the hepatic MCB were detected in group 2 where they were more pronounced on day 14. Blood flow rates in all parts of the MCB were lower than in the intact group.

It should be noted that the decreases in blood flow rates in postcapillaries of the hepatic MCB were in both test groups greater than in precapillaries.

The results presented above indicate that rheological properties of the blood and the hepatic microcirculatory system undergo marked alterations in the presence of two diseases which rapidly lead to irreversible changes associated with decompensation of adaptation mechanisms. As the analysis of our findings showed, rats with the acute toxic hepatitis superimposed on the alloxan-induced diabetes mellitus (group 1) were more severely ill than those in which the latter disease was superimposed on the former (group 2). The decreases in blood viscosity were not accompanied by improvements in hepatic blood flows in either group. In our previous experimental study [3], the recorded elevation of hydrostatic pressure in the hepatic MCB with development of a generalized vasodilation shortly after the induction of diabetes mellitus was found to result in increased permeability of hepatic sinusoids, which has been shown to cause accumulation of protein blood components in Disse's spaces [5]. Accumulating on the basement membrane along exchange microvessels, these components lead to "capillarization" of the sinusoids, aggravate the tissue hypoxia, and thus augment the damaging effect of heliotrine.

This study thus indicates that the combination of diabetes mellitus and acute toxic hepatitis was characterized by mutual intensification of the their pathogenic mechanisms, with rapid decompensation of adaptive responses. These mechanisms require further study at different levels, including the subcellular and molecular levels.

REFERENCES

1. A. F. Blyuger, *Klin. Med.*, No. 2, 51-59 (1987).
2. Kh. Ya. Karimov, in: *Topics of Current Interest in Medicine* [in Russian], Tashkent (1993), pp. 3-8.
3. Kh. Ya. Karimov, B. U. Iriskulov, and M. K. Ergashev, *Byull. Eksp. Biol. Med.*, **116**, No. 12, 584-585 (1993).
4. V. I. Udovichenko, *Pat. Fiziol*, No. 1, 73-75 (1978).
5. D. E. McMillan, *Microcirc. Endothelium Lymphatics*, **1**, No. 1, 3-34 (1984).
6. B. G. Stone and D. H. Van-Thiel, *Semin. Liver Dis.*, **5**, No. 1, 8-28 (1985).

Prevention of Immunosuppression in Stressed Mice by Altering the Activity of Neurotransmitter Systems

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The spleens of CBA mice stressed by being immobilized for 3 h in the supine position and then immunized with sheep erythrocytes showed evidence of immunosuppression manifested in reduced numbers of plaque-forming cells on day 4 and of rosette-forming cells on day 5 after the stress and immunization. The depletion of serotonin stores in the brain caused by p-chlorophenylalanine administered 48 h before stressing the animals abolished immunosuppression under the action of immobilization stress, and a similar effect resulted from the activation of postsynaptic dopamine receptors D_1 and D_2 by apomorphine injected at 30 min before stress. The prevention of immunosuppression observed to occur when the balance between the serotoninergic and dopaminergic systems was shifted so that the latter system became predominant, suggests that the stress reduces immune reactivity by altering the brain's neurochemical pattern and interfering with the mechanisms of neuroimmunomodulation.

Key Words: *stress; immunosuppression; serotoninergic and dopaminergic systems*

It is evident from what is currently known about relationships between the brain, psyche, and endocrine and immune systems [3,6,10,11] that impairment of the mechanisms underlying neuroimmunomodulation may result in altered immune reactivity. Immunological functions can be compromised by stressors of different kinds [8,15]. Although the neurochemical pattern of the brain after stressful exposure varies with the nature of stressor [1], serotonin synthesis and the activity of serotoninergic neurons increase in response to a number of stressors, including immobilization [8,9,12,13], while the dopamine level then remains unchanged or declines [4], but the rate of dopamine metabolism may rise in some brain structures [5]. Studies carried out at our institute have provided information on the importance for immune response development of a balance between the serononinergic (immunosuppressing) and dopaminergic (immunostimulating) systems at the time when antigen enters the body [3,11]. We showed also that a pharmacologically elicited elevation of the dopaminergic system's activity in stressed old C57Bl/6 mice can raise their immune response to the level characteristic of unstressed young animals [2]. Altering the brain's neurochemical pattern by pharmacological means may therefore be expected to open new avenues for preventing stress-induced immunosuppression.

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