DISTURBANCES OF THE MICROCIRCULATION AND OF VASO-TISSUE PERMEABILITY IN EXPERIMENTAL ACUTE DIFFUSE HEPATITIS

A. M. Chernukh and N. Ya. Kovalenko

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The dynamics of early disturbances of the microcirculation and vaso-tissue permeability was studied by intravital luminescence biomicroscopy during the development of acute diffuse hepatitis in rats produced by injection of allyl formate. Considerable dilatation of the microvessels with signs of stasis and microhemorrhages were observed. Vaso-tissue permeability was disturbed relative to albumins only. The biomicroscopic changes which developed occurred before damage to the parenchyma visible in the specimens.

The method of luminescence biomicroscopy of the internal organs suggested by the writers previously [1] was used to study the dynamics of early microcirculatory disorders and disturbances of vaso-tissue permeability during the development of acute diffuse hepatitis in rats.

EXPERIMENTAL METHOD

The toxic agent used was the specific capillary poison allyl formate which, according to the literature, produces acute inflammation of the liver in animals. The compound was injected intravenously in a dose of 0.0008 ml/100 g body weight. Parallel with the biomicroscopic investigations, the liver tissue was studied in specimens obtained at various times after injection of allyl formate (0.5, 1, 1.5, 2, and 3 h).

EXPERIMENTAL RESULTS

The biomicroscopic observations revealed the first signs of hemodynamic disturbances in the small vessels of the liver 10 min after injection of allyl formate. Capillaries in the region of the terminal afferent vessels were slightly dilated so that their diameter was equal to the diameter of the sinusoids in the region of the terminal hepatic venules. This was accompanied by slowing of the blood flow and the appearance of clumps of red cells in the microvessels. The phenomena described above gradually increase in severity so that 1 h after injection of the compound gross dilatation of microvessels was observed, the blood flow in them was slowed, and in some places an effect of complete stasis was produced. Foci of microhemorrhages were frequently seen in the region of the terminal afferent vessels. After 3 h the blood continued to flow virtually only in the zones adjacent to the terminal hepatic venules.

The following types of disturbances of the microcirculation were detected biomicroscopically during the development of acute diffuse hepatitis: 1) dilatation of the microvessels, most marked in the region of the terminal afferent vessels, with foci on microhemorrhages; 2) total and uniform dilatation of the sinusoids throughout the lobule; 3) dilatation of the microvessels only in the region of the terminal hepatic venule.

The types of microcirculatory disturbances described above were found in different parts of the liver of the same animal, interspersed with zones of visually normal appearance of the microvascular system.

Institute of Normal and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow.
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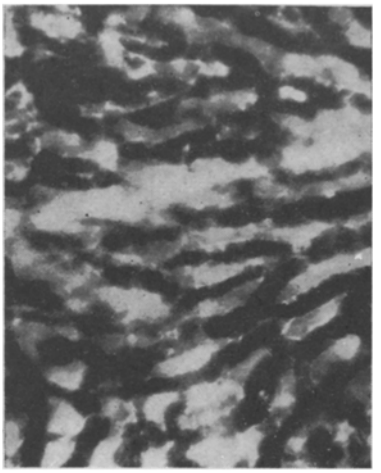

Fig. 1

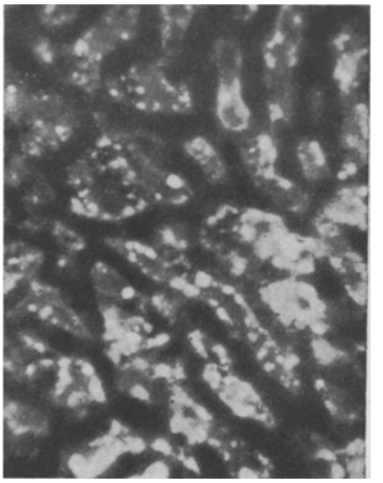

Fig. 2

Fig. 1. Liver of a rat with acute hepatitis 1.5 h after injection of allyl formate; diffuse permeation of liver cells with luminescent bovine albumen (75×).

Fig. 2. Liver of a rat with acute hepatitis 2 h after injection of allyl formate; luminescent vacuoles in cytoplasm of hepatocytes (75×).

This mosaic character of damage to the microvascular system of parenchymatous organs has also been observed in other types of pathology accompanied by damage to the tissue-blood barriers [3]. Lesions of the microvascular bed of the internal organs (particularly the liver) of this type are probably attributable to the physiological heterogeneity of individual parts of the organ, even at the level of its structural and functional units [4].

Heterologous luminescent proteins with different molecular weights were used as an indicator of the state of vaso-tissue permeability of the rat liver after the injection of allyl formate. Bovine albumin or globulin, labeled with fluorescein isothiocyanate, was injected intravenously 1 h after injection of the poison into the animals.

The writers showed previously [1] that luminescent heterologous proteins, if injected intravenously, can be found in the liver of intact rats only within the microvessels and in Kupffer cells, but they never penetrate into the cytoplasm of the hepatocytes.

After injection of heterologous luminescent proteins into animals with acute diffuse hepatitis, the following picture was observed. The appearance of labeled proteins in the microvessels of the affected liver was somewhat retarded compared with normal as a result of the development of stasis and foci of microhemorrhages. After injection of labeled albumen into the animals, individual brightly fluorescent hepatocytes, homogeneously permeated with protein, appeared within the first 10 min. As a rule they were found in the region of afferent terminal vessels (Fig. 1). Parallel with this, vacuoles of various sizes began to fluoresce in some hepatocytes. Finely dispersed dust-like luminescent granules appeared initially in the peripheral parts of the hepatocytes facing the sinusoids. The granules then became larger and began to resemble vacuoles of various sizes, still with a tendency to lie along the microvessels (Fig. 2). These cells were found only in the region of the afferent vessels or they occurred throughout the lobule. As a rule, the types of distribution of labeled protein in the hepatocytes correlated with the topography of the microcirculatory disturbances described above. In some cases the penetration of labeled albumen into the bile capillaries also was observed.

The dynamics of the distribution of labeled bovine globulin in the liver of rats with acute diffuse hepatitis differed significantly from that described above. Unlike the albumin, the labeled globulin remained entirely within the microvascular system as a luminescent juxtamural layer, clearly outlining the microarchitectonics of the dilated sinusoids.

Intensive fluorescence of the network of superficial lymphatics began to develop 5-10 min after the injection of luminescent proteins (albumins and globulins) into the experimental rats, and this fluorescence was more clearly defined above the region of the terminal afferent vessels.

A decrease in the phagocytic function of the Kupffer cells lining the microvessels in zones with a disturbed blood flow also was revealed biomicroscopically.

The microcirculatory disturbances during the development of acute hepatitis occurred before visible signs of injury to the parenchyma in the specimens. Visible changes did not appear until 1 h after intravenous injection of allyl formate. Loss of the normal tissue structure was observed in the region of the terminal afferent vessels, in places the endothelium of the microvessels was detached, and the Desse's spaces were somewhat widened. Individual endothelial cells appeared shrunken and pycnotic or, conversely, swollen and enlarged. Signs of necrosis were seen in some of the hepatocytes.

The changes described above gradually increased in severity, and after 3 h a distinct morphological picture of acute serous inflammation of the liver developed (gross dilatation of the Desse's spaces, desquamation of the endothelium, a marked disturbance of the normal structure of the liver, and necrosis of the hepatocytes).

A similar morphological picture was obtained previously after local injury to certain areas of the structural and functional unit of the liver by UV rays (microburns) [1]. However, biomicroscopy revealed a number of differences. For instance, during the development of acute diffuse inflammation the phase of constriction of the hepatic microvessels, so clearly observable after local injury of the liver, was absent. The hemodynamic changes after local exposure to UV rays were more severe: in the zone of injury practically no blood flow could be detected. Vaso-tissue permeability in diffuse hepatitis was changed relative only to albumins. In local inflammation, globulins also penetrate into the hepatocytes.

The differences in the course of the early phases of development of acute local and diffuse inflammation of the liver are difficult to explain on the basis of the writers' own observations and data published in the literature. Only a few hypotheses can be submitted.

The uniformity of the structural changes in the liver after exposure to UV rays and to the action of allyl formate is detectable only at the level of light-optical microscopy. In investigation of the liver at higher levels of integration of the organism (in particular, in ultrastructural analysis of the morphological disturbances) definite differences explaining the ways of penetration of the globulins and albumins into the parenchymatous cells of the liver in the acute phase of the inflammatory reaction can be detected.

The mechanism of the harmful action of the two agents chosen is different. In UV irradiation all cellular and subcellular structures of the irradiated zone of the structural-functional unit of the liver are damaged simultaneously, and a distinctive "paralysis of permeability" develops: the hepatocytes are permeated with proteins irrespective of their molecular weight. The biomicroscopic study shows that fluorescent material is not distributed along the course of the damaged sinusoids, but the whole of the affected parenchyma is simply permeated diffusely with luminescent globulin.

As the present observations and those of other authors show, during the toxic action of the capillary poison allyl formate the endothelium suffers first [2, 5], and changes in the parenchymatous cells develop somewhat later. This may indicate that during exposure to allyl formate only certain links in the chain of biochemical mechanisms of vaso-tissue permeability are affected and others remain intact. Because of this the hepatocytes (even if damaged) can evidently preserve some degree of selectivity of permeability, admittedly distorted pathologically, with respect to the protein molecule. Albumins penetrate into the parenchymatous cells while globulins remain in the microvessels.

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