FUNCTIONAL STATE OF THE LIVER IN EXPERIMENTAL STAPHYLOCOCCAL INFECTION

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UDC 616.981.25-092.9-07:616.36-008.1

In infection produced by intravenous injection of staphylococci of strain Wood-46 into albino rats, marked changes take place in the liver function and, in particular, the synthesis and liberation of bile acids are sharply inhibited. Their total concentration in the bile falls chiefly on account of taurocholic, glycocholic, and deoxycholic acids, whereas the concentration of cholic acid itself rises, evidently because of inhibition of the conversion of cholesterol into primary bile acids and conjugation of cholic acid with glycine and taurine. The hyperbilirubinocholia observed in the early periods of infection arises on account of hemolysis of the red cells.

KEY WORDS: staphylococcal toxin; rat liver; bile acids; cholesterol.

Previous investigations [1-3, 8] have shown that staphylococcal toxins have a marked hepatotropic action. In dogs, albino rats, and guinea pigs they reduce the intensity of bile secretion, inhibit the synthesis of bile acids, increase the concentrations of cholesterol and bilirubin in the bile, and disturb the stabilizing properties of the bile and motor activity of the extrahepatic bile ducts.

It was accordingly decided to study the state of the liver function in experimental staphylococcal infection and, in particular, the state of synthesis of bile acids and the excretion of cholesterol and bilirubin with the bile.

EXPERIMENTAL METHOD

Experiments were carried out on 75 male rats weighing 130-200 g. Staphylococcal infection was produced by intravenous injection of a 24-h culture of staphylococci of strain Wood-46 in a dose of 5×10^9 bacterial cells/100 g body weight. The development and duration of the infection were monitored by making squash preparations of the internal organs on nutrient agar and then identifying the growing cultures and also by measuring the body temperature and studying changes in the blood count.

On the 4th day of infection large numbers of staphylococci were seeded from the internal organs of the rats, whereas on the 8th and 15th days seedings from the heart and lungs were sterile, and positive cultures were obtained only from the kidneys, liver, and spleen. After infection the rats were apathetic, they lost their appetite, and responded feebly to external stimuli. The body weight fell, for example, from 184 ± 23 to 148 ± 18 g on the 15th day. The body temperature on the 2nd day of infection was increased by 1.5-2°C, and on the 8th day in most animals by 1°C. On the 8th day the red cell count was reduced by 27% but the white cell count was increased (from 15,620 to 21,250/mm^3). Consequently, staphylococcal infection when produced by this method in rats lasted more than 2 weeks.

The state of the liver function was determined both before infection (control), and on the 4th, 8th, and 15th days after infection by the method described previously [4], including chromatography of the bile.

Department of Pharmacology, Khar'kov Pharmaceutical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. R. Pokrovskii.) Translated from Byulleten Éksperimental'noi Biologii i Meditsiny, Vol. 78, No. 11, pp. 49-51, November, 1974. Original article submitted December 30, 1971.

EXPERIMENTAL RESULTS

During the 2 weeks of staphylococcal septicemia the intensity of the bile secretion showed no significant change. The level of bile secretion was depressed for only a short time – the first 3-4 days. In staphylococcal infection, and also in toxemia, mainly cholic formation, one of the principal processes in secretion, was inhibited. In particular, 3 days after infection the concentration of bile acids in separate hourly portions of bile did not exceed 766-500 mg% compared with 1214-475 mg% in the control; after 7 days the figure was 800-410 mg% and after 15 days it was 933-383 mg%. As a result, in the first period of observation the total quantity of bile acids was reduced by 35%. Later the excretion of cholates with the bile increased a little. Nevertheless, even 15 days after infection it had not reached its initial level. Both the formation of primary bile acids and their conjugation were inhibited. For instance, the concentration of taurocholic acid in the bile at all periods of observation was considerably reduced (on the average from 10.3 to 6.6, 7.1, and 7.8 mg/100 g body weight respectively, or by 36, 31, and 24%). The process of conjugation of cholic acid with glycine was disturbed even more. This stage of the cholate-forming process almost completely blocked throughout the period of infection, by 32% during the first period of observation, by 10% during the second, and by 49% during the third period.

By contrast with staphylococcal toxemia, during infection the conversion of deoxycholic into cholic acid was not significantly affected or was less severely disturbed. Cholic acid can be detected only as traces in the bile of healthy rats; i.e., its concentration is below 1-2 mg%. In staphylococcal infection, however, its concentration in certain hourly portions of bile increased to 4-8 mg% in the first period of observation, to 3-20 mg% in the second period, and to 5-21 mg% in the third period.

In staphylococcal infection, just as in staphylococcal toxemia, profound disturbances thus takes place in the synthesis of bile acids. The sharp decrease in the total cholate concentration in the bile points to inhibition of the conversion of primary bile acids (cholic and deoxycholic) from cholesterol. The decrease in the concentration of taurocholic acid and disappearance of glycocholic acid from the bile, associated with an increase in the cholic acid concentration, suggest that in this disease the formation of conjugation compounds of cholic acid with taurine and glycine is inhibited. This may take place either through a sharp decrease in the reserves of taurine and glycine in the liver or through inhibition of those biochemical reactions that are responsible for the conjugation of cholic acid with amino acids.

The cholesterol-excretory function of the liver was not significantly changed in staphylococcal infection, while the bilirubin excretion was intensified only during the first 4 days. The hyperbilirubinocholia, produced by staphylococcal infection and toxemia, was the result of the hemolytic action of the staphylococcal toxin.

In staphylococcal infection the colloid state of the bile was disturbed and conditions were created to cause precipitation of its components, as shown by a decrease in the ratio between conjugated and free bile acids and in the cholate–cholesterol ratio. Because of the smaller decrease in the cholate concentration compared with the increased relative cholesterol concentration in the bile, this last ratio was reduced at all periods of observation. In the first period it did not exceed a mean value of 40, in the second period 50, and in the third period 44 compared with a normal level of 65.

In staphylococcal infection the state of the liver function and, in particular, the synthesis of bile acids, are thus disturbed. Both the formation of primary bile acids and their conjugation with amino acids are inhibited. Inhibition of cholate formation and also, to a certain extent the hyperbilirubinocholia arising under these conditions, leads to a reduction in the stabilizing properties of the bile.

The inhibition of cholate formation in staphylococcal infection is evidently a result of the effect of the toxin on respiration and oxidative phosphorylation in the liver mitochondria. There are data in the literature to show that staphylococcal toxin reduces the intensity of respiration in the liver [5, 9], and the main source of the energy required for bile formation is tissue respiration coupled with oxidative phosphorylation [6, 7].

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