

EFFECT OF STAPHYLOCOCCAL TOXIN ON CHOLATE FORMATION

S. M. Drogovoz

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Staphylococcal toxin causes severe and prolonged inhibition of bile formation and of the synthesis of bile acids in albino rats. The decrease in cholate concentration in the bile takes place largely at the expense of taurocholic acid. The concentration of desoxycholic and cholic acids meanwhile increases. The toxin apparently inhibits biochemical processes responsible for the conversion of desoxycholic acid into cholic acid and of cholic acid into conjugated acids.

Previous investigations [1-3] have shown that in staphylococcal infections and toxicoses the formation and excretion of bile acids with the bile are inhibited in albino rats and guinea pigs. This action of the toxin is not usually manifested if, shortly before the experiment, it is treated with specific staphylococcal antiserum.

Having obtained these findings, the next step was to determine at the expense of which bile acids the concentration and total content of cholates in the bile were reduced, and to determine as far as possible the components of the cholate forming system on which staphylococcal toxin acts. The investigation described below was carried out for these purposes.

EXPERIMENTAL METHOD

Experiments were carried out on 60 albino rats of both sexes, weighing 130-180 g, by the method described previously [1, 6]. The following indices of intensity of bile excretion were used: A) the rate of bile secretion expressed in mg/min/100 g body weight, and B) the total volume of secretion obtained every hour and during the 10 h of the experiment (in mg/100 g body weight). Hourly samples of bile were collected and tested to determine the concentration (in mg%) and total content (in mg/100 g body weight) of total bile acids and then separately of taurocholic, glycocholic, cholic, and desoxycholic acids. The bile acids were fractionated by ascending paper chromatography [4, 5], and their concentrations were determined colorimetrically by Karbach's method [4].

In the first two series of experiments the initial background of bile secretion and cholate formation was established in healthy male and female rats, and in the remaining series the effect of staphylococcal exotoxin, isolated by the writer from strain Wood-46 and of toxin obtained from the N. F. Gamaleya Institute of Epidemiology and Microbiology (Batch No. 590) on these processes was determined.

EXPERIMENTAL RESULTS

Under the influence of toxin isolated from strain Wood-46, in a dilution of 1 : 30 (0.5 ml/100 g body weight, intravenously), only moderate inhibition of bile secretion took place in female rats, on the average from 4.4 ± 0.3 - 3.5 ± 0.2 to 3.2 ± 0.3 - 3.1 ± 0.2 mg/min/100 g. In this case the figure for the total quantity of bile produced in 10 h was reduced from 2268 to 1944 mg/100 g, or by 14.3%. With an increase of 50% in the dose of toxin, its anticholeretic action was strengthened: the rate of bile secretion was reduced to 2.9 ± 0.2 - 2.6 ± 0.2 mg/min/100 g ($P < 0.01$ and < 0.02 , respectively), and the total content of bile was reduced to 1734 mg/100 g, or by 23.6%. The changes affecting the cholate content in the bile also differed. Under the in-

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fluence of toxin in a larger dose the cholate concentration fell in nearly all hourly portions of bile, while in a smaller dose the cholate concentration fell only in the first three portions and was increased in the rest. As a result of this, following injection of toxin in a dilution of 1 : 30, the total content of cholates excreted with the bile in 10 h remained almost unchanged, but it was reduced if the toxin was injected in a dilution of 1 : 20 (on the average from 14.269 to 10.939 mg/100 g body weight, or by 23.3%). The decrease in concentration of cholates took place mainly on account of taurocholic acid, the total content of which fell after administration of the larger dose of toxin from 12.304 to 8.334 mg/100 g, or by 32.3%. A sharp decrease in the concentration of glycocholic acid, amounting in some cases to its total disappearance, also was observed, especially after injection of toxin in a dilution of 1 : 20. The total content of this acid fell from 0.32 to 0.11 mg/100 g if the toxin was given in a dilution of 1 : 30, and to 0.039 mg/100 g if in a dilution of 1 : 20.

Meanwhile a marked increase was observed in the content of desoxycholic acid in the bile. In individual hourly portions its concentration rose from 89-20 to 119-54 mg% following injection of the smaller dose of toxin and to 192-24 mg% after injection of the larger dose. Such a considerable increase in the concentration of desoxycholic acid led to an increase in its total content: in the first case from 0.948 to 1.678 mg/100 g and in the second case to 1.746 mg/100 g, or by 77 and 85%, respectively.

The intensity of bile secretion and cholate formation was disturbed to an even greater degree in male rats with acute staphylococcal poisoning produced by injection of toxin obtained from the N. F. Gamaleya Institute (0.35 mg/100 g body weight, intravenously). The quantity of bile excreted in this case was 33.5% less than in the control. In turn, the concentration of cholates was usually increased in most of the hourly portions of bile, although admittedly not to any great degree. However, because of the low level of intensity of secretion, the total content of bile acids secreted fell on the average from 16.806 to 13.35 mg/100 g, or by 20.7%. This decrease took place largely on account of taurocholic acid.

The content of the second conjugated acid (glycocholic) was increased from 0.494 to 0.802 mg/100 g, i.e., by almost twice. The content of desoxycholic acid, on the other hand, as in the female rats, was increased on the average only from 1.196 to 1.505 mg/100 g.

The fourth bile acid (cholic) is contained in the bile of healthy rats in very small amounts, as traces. However, in staphylococcal poisoning, especially if due to toxin obtained from strain Wood-46, its concentration at the end of the experiment had increased to 5-12 mg%.

The results of these experiments thus show that the decrease in content of cholates in the bile of rats with acute staphylococcal poisoning takes place largely on account of taurocholic acid, that which is most representative of this species of animal. The concentration and total content of desoxycholic acid also were increased, and in the case of severe poisoning, those of cholic acid also.

According to some workers [7-9], desoxycholic acid in albino rats is an intermediate product of conversion of cholesterol into cholic acid. Since in the present experiments the decrease in content of cholates in the bile occurred against a background of an increase in desoxycholic acid concentration, the most important point of action of staphylococcal toxin on cholate formation must evidently be the inhibition of biochemical processes responsible for the conversion of desoxycholic into cholic acid. In addition, staphylococcal toxin also inhibits to some extent the conversion of cholic acid into conjugated acids. Evidence of this is given by the increased content of cholic acid in the bile.

This, of course, is not the only effect of staphylococcal toxin on cholate formation, because in addition to the facts described above, changes were also observed in the content of glycocholic acid in the bile. The dissimilar character of these changes (an increase under the influence of one type of toxin and a decrease under the influence of another) may be attributed to the nonidentity of the toxins studied.

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