FACTORS PRODUCING BILE INFARCTION AND BILE DUCT PROLIFERATION IN BILIARY OBSTRUCTION

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SUMMARY

To clarify the factors producing bile infarction and bile duct proliferation in obstructive jaundice, the incidence of the hepatic lesions and the serum levels of the bile constituents were examined in three rat models. (1) Ligation of the common bile duct induced bile infarction, bile duct proliferation, retention of bile in the liver, and elevation of the serum levels of total bilirubin and total bile acids. (2) The rats treated by choledochotomy had bile in the abdominal cavity, but there was no retention of bile in the liver. The degree of development of bile infarction was similar to that of the common bile duct ligation group, but bile duct proliferation was not found: the serum levels of total bilirubin and total bile acids were elevated. (3) In the rats subjected to partial bile duct ligation, bile infarction and bile duct proliferation were seen only in the lobes with ligation of the hepatic ducts: only slight or no elevation of the serum levels of total bilirubin and total bile acids was found. These data suggest that bile infarction is caused by the toxic action of bile constituents other than bilirubin and bile acids. absorbed into the blood from the obstructed biliary system, and that bile duct proliferation is due to mechanical factors following bile retention or direct actions of retained bile in the liver.

KEY WORDS—Bile infarction, bile duct proliferation, biliary obstruction, obstructive jaundice, bilirubin, bile acids.

INTRODUCTION

It is well known that biliary obstruction induces bile infarction and proliferation of bile ductules and ducts.1-5 It is generally thought that the development of bile infarction requires two factors: a toxic chemical factor, the stagnant bile, and a mechanical co-factor, the raised biliary pressure.6,7 The proliferation of bile ducts appears to be caused mainly by mechanical dilatation of the ducts.8 However, these hypotheses are controversial because they were established mainly by using the common bile duct-ligated animal model, which has retention of bile, impairment of trans-hepatocellular transport of bile constituents, and increased biliary pressure. Two further rat models were therefore used in the present study. One is the rat treated with choledochotomy, which is characterized by retention of bile in the abdominal cavity without impairment of bile flow. The other is the rat treated with ligation of hepatic ducts of only the left lateral lobe and the median lobe. To clarify the factors producing the hepatic lesions after obstructive jaundice, the relationship between the degree of the hepatic lesions and the liver function tests were examined in these two models and compared with those in the rats with complete biliary obstruction.

MATERIALS AND METHODS

Male Wistar rats weighing about 200 g were used. The animals were kept on a standard pellet diet and had free access to tap water throughout the experiments. The abdomen was opened through an upper midline incision under light ether anaesthesia and with aseptic operative techniques. The common bile duct at the liver hilum was exteriorized by gentle manipulation.

Group A (N = 28): Sham operation. Two silk threads were placed loosely around the common bile duct.
Group B (N = 40): Common bile duct ligation. The common bile duct was tied in two places and divided.

Group C (N = 18): Partial bile duct ligation. The hepatic ducts of the left lateral lobe and the median lobe were tied in two places and divided. The hepatic ducts of other lobes, the right median lobe, the right lateral lobe, and the caudate lobe, were kept intact. Naming of lobes of the rat liver conformed to those of Farris and Griffith.

Group D (N = 17): Choledochotomy. The common bile duct was tied in one place and cut off at the hepatic side of the ligature.

The abdomen was reopened 3 days after the operation under light ether anaesthesia. Blood samples for liver function tests were taken. Immediately after blood sampling the liver was removed, fixed in 10 per cent neutral formalin, and embedded in paraffin. Sections were stained with haematoxylin and eosin for histopathological examination. Grades of bile infarction and bile duct proliferation were evaluated without knowledge of the experimental conditions as follows: -, no; +, slight; ++, moderate; +++, severe.

Data are expressed as the means ± SD and were analysed statistically by Student's t-test. The level of significance was P < 0.05 for all experiments.

RESULTS

Body weight, liver weight, and data of the liver function tests in each experimental group are shown in Table I. The incidence of bile infarction and bile duct proliferation is given in Table II.

In the group which had undergone a sham operation, the liver appeared normal macroscopically and histologically. The liver function tests were within the normal limit.

Ligation of the common bile duct induced a remarkable elevation of the serum levels of transaminases, alkaline phosphatase, total bilirubin, total bile acids, and total cholesterol. The liver was slightly enlarged, and the common bile duct at the liver hilum, the hepatic ducts, and the intrahepatic large bile ducts were dilated and contained large amounts of bile. Feathery degeneration of hepatocytes and bile infarction appeared sporadically in the lobules with no topographical relationship (Fig. 1). The bile infarcts often contained foamy lipid-laden phagocytes, mononuclear cells, and neutrophils. Single liver cell necroses and acidophilic bodies were also found sporadically. The degree of development of bile infarction did not relate to the serum levels of total bilirubin or total bile acids (Figs 2 and 3). Bile duct proliferation enlarged the portal triads (Fig. 4). This was accompanied by fibroblastic proliferation and infiltration of a small number of neutrophils and mononuclear cells. The proliferated ducts had a recognizable lumen lined by cuboidal cells, and mitoses appeared in the lining cells. There was no relationship between the degree of bile duct proliferation and the serum levels of total bilirubin or total bile acids (Figs 5 and 6). The degrees of bile infarction and bile duct proliferation in the left lateral and median lobes were slightly more severe compared with those of other lobes.

In the rats subjected to partial bile duct ligation, the liver weight and the serum levels of transaminases, total bile acids, alkaline phosphatase, and total cholesterol were slightly elevated compared with those of the sham operation group, except for bilirubin. The macroscopic and microscopic findings of the left lateral lobe and the median lobe were essentially similar to those of the common bile duct ligation group. On the other hand, in the right median lobe, the right lateral lobe, and the caudate lobe, bile infarction and bile duct proliferation were not found in many cases.

The rats which experienced choledochotomy had 5–30 ml of a yellowish fluid without infection in the abdominal cavity. There was no dilatation of the common bile duct. The body weight and liver weight were decreased as compared with those of the sham operation group. The serum levels of transaminases, total bilirubin, total bile acids, and total cholesterol were elevated. The degree of development of bile infarction was similar to that of the common bile duct ligation group, but bile duct proliferation was not found in many cases.

DISCUSSION

Bile infarction is diagnostic for extrahepatic cholestasis, although small areas of such necrosis can also occur in intrahepatic cholestasis. It is generally thought that bile infarct after obstruction of the common bile duct is probably due to two factors: a mechanical factor—increased biliary pressure and interference with the blood circulation by the dilated bile ducts, and a chemical factor in the bile—bile salts. However, it is reported that bile infarction occurs not only in the members of parabiotic pairs subjected to common bile duct ligation, but also in the non-jaundiced partners without obstruction of the common bile duct. Moreover, foci of
Table I—Body weight, liver weight, and liver function tests

<table>
<thead>
<tr>
<th></th>
<th>Body weight (g)</th>
<th>Liver weight (g)</th>
<th>SGPT (U/l)</th>
<th>SGOT (U/l)</th>
<th>Total bilirubin (mg/dl)</th>
<th>Total bile acids (μmol/l)</th>
<th>Alkaline phosphatase (KAU)</th>
<th>Total cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Sham operation</td>
<td>28</td>
<td>228 ± 15</td>
<td>8.3 ± 1.2</td>
<td>52 ± 15</td>
<td>171 ± 32</td>
<td>0.10 ± 0.07</td>
<td>13.1 ± 10.6</td>
<td>30.2 ± 6.1</td>
</tr>
<tr>
<td>B. Common bile duct ligation</td>
<td>40</td>
<td>225 ± 18</td>
<td>10.6 ± 1.2*</td>
<td>186 ± 74*</td>
<td>479 ± 164*</td>
<td>12.69 ± 3.52*</td>
<td>581.7 ± 197.6*</td>
<td>40.5 ± 8.3*</td>
</tr>
<tr>
<td>C. Partial bile duct ligation</td>
<td>18</td>
<td>236 ± 28</td>
<td>9.9 ± 2.0*</td>
<td>73 ± 30*†</td>
<td>211 ± 82†</td>
<td>0.14 ± 0.09†</td>
<td>37.0 ± 18.6*</td>
<td>41.4 ± 8.5*</td>
</tr>
<tr>
<td>D. Choledochotomy</td>
<td>17</td>
<td>202 ± 19*†</td>
<td>6.7 ± 0.6*</td>
<td>66 ± 20*†</td>
<td>314 ± 103*†</td>
<td>2.54 ± 1.13*†</td>
<td>277.4 ± 69.9*†</td>
<td>23.1 ± 8.2*†</td>
</tr>
</tbody>
</table>

Values are means ± SD. N = Number of rats; SGPT = serum glutamic-pyruvic transaminase activity; SGOT = serum glutamic-oxaloacetic transaminase activity.

*P < 0.05, compared with the group of sham operation.
†P < 0.05, compared with the group of common bile duct ligation.
‡P < 0.05, compared with the group of partial bile duct ligation.
Table II—Incidence of histopathologic features in the liver

<table>
<thead>
<tr>
<th>Grade of bile infarction</th>
<th>Grade of bile duct proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>A. Sham operation</td>
<td>28 (1)</td>
</tr>
<tr>
<td>(2)</td>
<td>28</td>
</tr>
<tr>
<td>B. Common bile duct ligation</td>
<td>40 (1)</td>
</tr>
<tr>
<td>(2)</td>
<td>8</td>
</tr>
<tr>
<td>C. Partial bile duct ligation</td>
<td>18 (1)</td>
</tr>
<tr>
<td>(2)</td>
<td>14</td>
</tr>
<tr>
<td>D. Choledochotomy</td>
<td>17 (1)</td>
</tr>
<tr>
<td>(2)</td>
<td>4</td>
</tr>
</tbody>
</table>

N = Number of rats.
(1): The left lateral lobe and the median lobe.
(2): The right median lobe, the right lateral lobe, and the caudate lobe.
- = No; + = slight; ++ = moderate; +++ = severe.

Fig. 1—The liver of a rat 3 days after ligation of the common bile duct. Bile infarction with infiltration of a small number of neutrophils and mononuclear cells.

Fig. 2—Relationship between the degree of bile infarction and the serum level of total bilirubin in rats 3 days after ligation of the common bile duct.

Hydropic degeneration and necrosis of hepatocytes also occur in the rats treated with choledochocaval fistula. Accordingly, it is not clear whether the mechanical factor is necessary for the development...
Fig. 3—Relationship between the degree of bile infarction and the serum level of total bile acids in rats 3 days after ligation of the common bile duct.

Fig. 4—The liver of a rat 3 days after ligation of the common bile duct. Proliferation of the bile duct extends the portal triad.

Fig. 5—Relationship between the degree of bile duct proliferation and the serum level of total bilirubin in rats 3 days after ligation of the common bile duct.

Fig. 6—Relationship between the degree of bile duct proliferation and the serum level of total bile acids in rats 3 days after ligation of the common bile duct.
of bile infarction, or what the toxic components of the retained bile are.

The present study clearly demonstrates that bile infarction develops not only in the rats which experienced common bile duct ligation, but also in the rats treated by choledochotomy. This indicates that the mechanical factor—increased biliary pressure and dilatation of bile ducts—is not necessary for the development of bile infarcts. Moreover, it is obvious that the bile constituents absorbed into the blood from the abdominal cavity contribute to the development of bile infarction in rats treated by choledochotomy. It is well known that bile infarcts of bile infarction in rats treated by choledochotomy. This indicates that proliferation of bile ducts after biliary obstruction relates to a mechanical factor, increased biliary pressure and dilation of bile ducts, or the direct action of retained bile in the liver, but not to the bile constituents absorbed into the blood.

In summary, it is thought that bile infarction in extrahepatic biliary obstruction is caused by the toxic action of bile constituents absorbed into the blood from the obstructed biliary system, and that proliferation of bile ductules and ducts is due to a mechanical factor following bile retention or the direct action of retained bile in the liver.

REFERENCES