Effect of Cholecystoduodenostomy and Choledochostomy in Pancreatic Carcinogenesis

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ABSTRACT

The pancreatic carcinogen N-nitrosobis(2-oxopropyl)amine was administered to Syrian golden hamsters after cholecystoduodenostomy and choledochostomy to investigate a possible bile reflux mechanism as a factor in pancreatic carcinogenesis. The induced lesions were similar in morphology, multiplicity, and distribution to those of animals in other studies without surgery. Hence the findings contraindicate the importance of bile reflux in pancreatic tumor induction. Other possible mechanisms are discussed.

INTRODUCTION

Among the etiological factors in pancreatic cancer, the bile reflux mechanism is presently the most popular hypothesis (9) and stems from the observation that most clinical pancreatic cancer develops in the head of the organ, in which bile-borne carcinogen could be effective. Although in hamsters the induced pancreatic neoplasms were randomly distributed among different pancreatic segments, much cancer developed in the pancreas head around the collecting main ducts (6, 7). This preferred cancer site was postulated to be due to the effect of either bile-borne or pancreatic juice-borne carcinogen. In the former case the bile reflux mechanism could be responsible, whereas in the latter it may be caused by a higher concentration of the carcinogen in the main collecting ducts in the head of the organ. In the present study the significance of bile reflux mechanism in pancreatic carcinogenesis was investigated in cholecystoduodenostomized and choledochostomized Syrian golden hamsters.

MATERIALS AND METHODS

Surgical Techniques. (For the anatomy and topography of the bile and pancreatic ducts in hamsters, see Ref. 8.) Under pentobarbital anesthesia (75 mg/g body weight) an approximately 2-mm-long segment of the common bile duct was dissected between 2 ligations (with silk suture) on the distal portion of the common bile duct just above the opening of the pancreatic duct (Chart 1a). A 2- to 3-mm-long incision was made in the gallbladder fundus near the silk thread for bile flow (Chart 1a), and the gallbladder was then inserted into the duodenal lumen through a wound 5 to 10 mm distal to the opening of the common duct and secured by tightening the silk threads through a knot (Chart 1b). In 2 hamsters an operative cholangiogram through the duodenostomy prior to closure was performed to demonstrate the integrity of the anastomoses. By this method no contrast medium was visible in the common duct (and pancreatic ducts). Animals were treated during the next consecutive 3 days with Terramycin (Pfizer Inc., New York, N. Y.) in drinking water (0.1% solution). Only animals in normal condition 7 days after the operation were included in the experiments. Three hamsters were killed after 3 weeks for histological examination of surgical effects.

RESULTS

Effects of Surgery. The weight lost by animals due to surgery was rapidly regained during the first postoperative week. Thereafter, no remarkable differences were clinically observed between these and control hamsters (of other parallel experiments). Three weeks after surgery the gallbladder in each of 3 sacrificed hamsters was found to have disappeared, and a free and intact communication between the cystic duct and duodenal lumen was observed (Chart 1c; Fig. 1). The epithelial lining of the intra- and extrahepatic duct system was intact.

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1. Por, P. K. (1974) Cancer Res. 34, 2048-2051. 2. To whom requests for reprints should be addressed, at Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, Nebr. 68105. Received January 9, 1978; accepted April 14, 1978.
and the incidence and sites of induced neoplasms are summarized in Table 1. All treated hamsters developed pancreatic neoplasms, which were classified as adenomas (50 and 33%), intraductal carcinomas (60 and 0%), and adenocarcinomas (100 and 67% in Groups 1 and 2, respectively). Adenomas (up to 50 in Group 1 and 15 in Group 2) were usually found in hamsters exhibiting fewer adenocarcinomas that had not destroyed the pancreatic tissue. However, in 50% of Group 1 animals, the entire pancreas was occupied by adenocarcinomas of various sizes (1 to 16 mm) and numbers (on the average, 11 tumors/animal with a range of 2 to 20 tumors/pancreas). In 4 hamsters the tumors had coalesced to about 4-cm-large nodules (Fig. 2). In 5 animals these lesions had invaded the peripancreatic lymph nodes, and in 1 animal they had invaded the spleen, liver, and entire peritoneum. Distant metastases were not found. Animals with larger numbers of tumors often exhibited serosanguinous ascites (5 to 50 ml), and nearly all had watery intestinal contents at death; this was not seen in controls. The localization of pancreatic neoplasms was in accordance with previous studies (3, 6, 7) and predominated in the tail of the splenic lobe and along the main ducts. Also, analogous to previous findings (3, 6, 7), > 90% of all tumors had ductular patterns, most of which arose from intra- and perinsular ductules. In animals subjected to a single BOP injection, peri- and intrainsular ductular proliferations were the primary findings; 1 ductular carcinoma in situ in a hamster of this group had developed within the islet (Fig. 3). Hyperplasia and metaplasia of the pancreatic ductal epithelium and marked papillary proliferation of the common duct epithelium (Fig. 4) were found in all Group 1 animals and, to a much lesser extent, in Group 2 hamsters. Hyperplasia of the common bile duct stump and occasionally also of the hepatic duct occurred only in 3 hamsters of Group 1, 2 of which showed marked distension and papillary proliferation.

Proliferation of the small intrahepatic bile ducts, hyperplasia, and often goblet cell metaplasia of the larger hepatic ducts were found in all treated hamsters, but cholangiomas were found only in those of Group 1. Similarly, hyperplasia and dysplasia of bronchial epithelium and alveolar hyperplastic nodules (up to 5 in number) and 1 alveologenic adenoma were found only in Group 1 hamsters. Tumors of other sites included a forestomach papilloma (Group 1 at 25 weeks) and parathyroid adenoma (control at 24 weeks).
DISCUSSION

Compared to previous results (2, 3, 6, 7) the distribution and patterns of BOP-induced pancreatic neoplasms in this study were not altered by bypassing the bile through the common duct. Consequently, the effect of bile can be excluded as a mediating factor in pancreatic carcinogenesis. In the present study the possible regurgitation of bile-borne carcinogen from the duodenum into the pancreatic duct is most unlikely because in this species the pancreatic ducts enter the common duct well before it opens into the duodenum (8) and because no evidence for such a reflux could be demonstrated by cholangiograms. Nevertheless, in view of the similar location and morphology of these induced pancreatic lesions (especially with regard to the marked papillary proliferation of common duct epithelium), compared to previous findings, mechanisms other than bile reflux seem to operate in experimental pancreatic tumor induction.

In this as well as in previous experiments (2, 6, 7), most induced pancreatic tumors were of ductular origin, and many seemed to develop within or around the islets (for definition see Refs. 2 and 7). The preference for the peri- and intralobular ductules as sites of cancer induction could well be due to a greater exposure of the responsive ductular cells to the blood-borne carcinogen because of a marked vascularity of islets. This would explain why limited or single BOP doses in previous studies (2, 6, 7) and in this experiment primarily affected the intra- and perilobular ductules. Further support for a direct blood-mediated carcinogenic effect of BOP in the pancreas was found after p.o. BOP administration, which resulted in induction of only a few pancreatic tumors but a 100% incidence of liver neoplasms, apparently due to the primary effect of carcinogen in the liver (4). On the other hand, compared to BOP, lower equitoxic doses of N-nitrosobis(2-hydroxypropyl)amine and N-nitrosobis(2-acetoxypropyl)amine applied locally to the skin and vagina led to larger numbers of pancreatic tumors, mediated presumably by local absorption of carcinogen (5). Since the few pancreatic neoplasms induced after p.o. BOP application were primarily found around the main duct in the head region (4) and since there was a relationship between the severity (and extent) of the alteration of these ducts and the BOP dose (2, 6, 7), it could be assumed that this pattern reflects an additional transluminal neoplastic effect of carcinogen and/or its metabolites excreted via pancreatic juice. Accordingly, the concentration of carcinogen would be higher in the large collecting ducts of the pancreas head, an assumption partially supported by common metabolites of pancreatic carcinogens identifiable in pancreatic secretions (1).

Although extrapolation of these experimental results to humans is still premature, there are circumstances that relate well to the human situation. For instance in the experimental model there was a direct correlation between the number of induced tumors and the size (and weight) of the pancreatic segments from which the tumors arose (7). The same situation could conceivably apply to humans since the pancreas head in humans constitutes a larger tissue mass. Consequently, the higher tumor incidence in this pancreas portion would be self-explanatory.

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