NOTE

Biliary Epithelial Abnormality Induced in Mice by Repeated Intraperitoneal Injections of Swine Serum

Kazuyuki KITAMURA, Akira YASOSHIMA, Hitoshi O. IWASAKI, Kunio DOI, and Azusa OKANIWA

Biological Research Laboratory, Tanabe Seiyaku Co., Ltd., Kawagishi, Toda, Saitama 335, and 1Faculty of Agriculture, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113, Japan

(Received 5 July 1984/Accepted 12 December 1984)

ABSTRACT. The livers of the male ddY mice having received repeated intraperitoneal injections of sterile swine serum were examined pathologically. The characteristic changes were eosinophilic and homogeneous or needle-shaped materials in the cytoplasm of biliary epithelial cells. Electron microscopically, the homogeneous material appeared moderately electron dense and amorphous being deposited in remarkably dilated rough-surfaced endoplasmic reticulum, while the needle-shaped one was quadrate in overall shape showing striated crystalline arrays at high magnification. —KEY WORDS: Biliary epithelial abnormality, Mouse.

Kitamura et al. [2] have described pathomorphology of hepatic fibrosis in the rats repeatedly injected with swine serum. From the viewpoint of comparative pathology, the mice treated in a similar manner were examined in the present study.

A total of 100 male ddY mice, 4 weeks of age, weighing about 25.3 g, were used. Seventy of them received intraperitoneal injections of 0.25 ml of sterile swine serum (Irvine Scientific, Inc., Lot No. 907524) twice a week. After three or four injections, most animals exhibited such anaphylactic symptoms as congestion of the auricles and tail and sedation. Ten animals died within 10 min after the 3rd injection and other six after the 4th one (cumulative mortality, 22.9%). On the second day after two, four, six, eight, 16 and 24 injections, seven to 10 animals each were sacrificed. Five animals each out of thirty controls injected intraperitoneally with saline were sacrificed at the same intervals. The liver was fixed in a 10% buffered neutral formal solution. Paraffin sections were subjected to staining by different methods as shown in Table 1. For electron microscopy, small blocks of the liver were fixed in 2.5% glutaraldehyde and 1% osmium tetroxide and processed by the routine method.

Microscopically, no alteration was detected in any animal after the 2nd injection. In six of seven animals after the 4th injection, infiltration of many eosinophils and a few mononuclear cells was seen in the portal tracts. The epithelial cells of some large-siz-
ed intrahepatic bile ducts were swollen with accumulation of eosinophilic, homogeneous material in their cytoplasm and some of their nuclei atrophied. These large-sized intrahepatic bile ducts contained cellular debris in their lumina, and fibroblasts and collagen fibers increased in number around the ducts. In all animals after six or more injections, biliary epithelial changes were also distributed everywhere in sections. In some bile ducts, eosinophilic, needle-shaped materials were observed in their lumina and in the cytoplasm of epithelial cells (Fig. 1). These needle-shaped materials gave the same staining properties as did the eosinophilic, homogeneous material in various staining methods (Table 1). At this point of time, epithelial cells of the gallbladder showed the same changes as those observed in the intrahepatic bile ducts. There was no noticeable change in hepatocytes of any mouse.

Electron microscopically, the epithelial cells of the intrahepatic bile ducts after the 2nd injection were irregular in shape and size, and the intercellular spaces were dilated. Large autophagic vacuoles and proliferation of segmentally dilated rough-surfaced endoplasmic reticulum (rER) were marked in these cells (Fig. 2). After four or more injections, dilatation of rER in the epithelial cells was more conspicuous. The cisterna showed a round profile due to accumulation of a large amount of amorphous material seemingly corresponding to the eosinophilic, homogeneous material observed by light microscopy (Fig. 3). Moderately electron-dense quadrate structures edged with membranes were often observed in the vicinity of dilated rER in some epithelial cells (Fig. 4). These struc-
BILIARY EPITHELIAL ABNORMALITY IN MICE

Fig. 3. An intrahepatic bile duct after eight injections. The cytoplasm of the epithelial cells is occupied with markedly dilated rER (*). Irregularity is noted in the arrangement of epithelial cells. ×2,500.

Fig. 4. The epithelium of an intrahepatic bile duct after eight injections. Quadrate structure (arrows) is found in the vicinity of dilated rER (*) in the cytoplasm. ×10,400.

tures showed striated crystalline arrays at equal spaces of 4 nm, which apparently corresponded to the eosinophilic, needle-shaped material observed by light microscopy. From the site and sequence of occurrence and staining characteristics, the needle-shaped materials may have resulted from crystallization of eosinophilic, homogeneous material originally formed in rER.

Such accumulation of amorphous material in rER has been reported in the atypical acinar cells of the human pancreas [3], follicular epithelial cells of thyroid glands [4] and thyrotrophs in anterior pituitary gland [5] in the rat treated with sulfonamide, pancreatic acinar cells in the dog treated with caerulein [6] and plasma cells containing Russell bodies [1]. In all these cases, each cell concerned had active function of protein synthesis under normal condition and such changes were considered to be a morphological manifestion of excess protein synthesis or suppressed or impaired protein secretion in these cells. In the present study, the appearance of homogeneous material in dilated rER and crystalline structures in the biliary epithelial cells may be attributed to an abnormality in protein synthesis though the mechanisms are still unknown.

REFERENCES

要約

プタ血清を反復投与したマウスに見られた胆管病変（短報）：北村和之・六十島昭・岩崎 仁・土井邦雄・岡垣 柊（田辺製薬株式会社生物研究所、東京大学薬学部）——無菌プタ血清を繰り返し腹腔内投与したマウス肝胆管系上皮細胞に好酸性硝子様物質および針状の好酸性結晶物質が出現した。前者は電顕的に槽の著しく拡張した粗面小胞体内に貯留した不定形物質で、後者は粗面小胞体に接して位置し、強拡大で規則正しい網状結晶配列を示す方形物質であった。