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ELECTRON MICROSCOPIC OBSERVATION OF THIORIDAZINE-INDUCED HEPATITIS

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The introduction of new drugs for clinical practice in recent years, has caused an increasing number of drug-induced hepatic injuries, which are currently receiving much attention because of their iatrogenic nature. As one of the approaches to the study of pathogenesis, electron microscopic studies have been undertaken. This report is concerned with an electron microscopic observation of the liver of a thioridazine-induced hepatitis patient with special reference to the bile canalicular alterations.

MATERIALS AND METHODS

The liver biopsy specimen was obtained from a 24 year old female with symptoms of jaundice, skin rash and itching which developed after receiving a 300 mg daily dose of Thioridazine for 7 days. The liver function tests at the time of liver biopsy indicated serum bilirubin 4.5 mg of which direct 3.8 mg, GOT 325 u, GPT 470 u, alkaline phosphatase 6.0 Bessy u. and cholesterol 250 mg percent and the blood examination showed a marked eosinophilia.

For electron microscopy, the liver specimen was fixed in a cold 1 percent osmium tetroxide solution, buffered to ph 7.4 with sodium veronal acetate. The specimen was then dehydrated in graded alcohols and propylene oxide, and embedded in Epon 812. Ultra-thin sections were cut with a glass knife on a Porter-Blum microtome, stained with lead hydroxide and uranyl acetate, and examined in a HU-11 A electron microscope.

RESULTS

1) Light microscopic observation (Fig. 1)

The changes of the liver cell were minimal and bile plugs of moderate degree were observed especially in the centrolobular area. Mild round cell infiltration with slight proliferation of the bile ductule was noted in the portal area.
The changes of the liver cell are minimal, except presence of bile plugs of moderate degree especially in the centrolobular area.

Round cell infiltration with slight proliferation of the bile ductule is noted in the portal area.

2) Electron microscopic observation (Fig. 2, 3, 4 and 5)
Under the electron microscope, the most striking changes were noted in and around the bile canaliculus. Most of the bile canaliculi were irregularly dilated with loss or shortening of its microvilli and edematous microvilli forming blebs were occasionally observed; in the lumen an electron-dense bile plug, granular, crystalline-like or laminated in appearance, was frequently seen. Some of those bile plugs
The bile canaliculus is markedly dilated with loss or stunt of its microvilli. One microvillus shows to be edematous and protruded into the lumen. A portion of the cytoplasmic band of the liver cell facing the canaliculus is demarcated by a linear border (at arrow). The nucleus, mitochondria and endoplasmic reticulum reveal no conspicuous changes.

A cytoplasmic band of the liver cell facing the bile canaliculus filled with bile plug was denser and devoid of vesicles and free ribosomes and a part of the cytoplasm facing the bile canaliculus was occasionally demarcated by a dense linear border. The Golgi apparatus was scant in number around the bile canaliculus filled with bile, but was well developed around the empty canaliculus.

Another remarkable change was the accumulation of electron dense granules, presumed to be bile or a lipid-containing component in the cytoplasm of the liver cell, especially around the bile canaliculus. They appeared to be mostly laminated or granular in vacuoles of sizes ranging from 0.2 to 2.0 μ. Such electron dense materials were also observed in the Kupffer cell which was mildly enlarged and contained a large number of pinocytic invaginations of the cell membrane.

The lysosomes appearing to be less dense and homogenous in the matrix were considerably increased in some of the liver cell cytoplasm. The nucleus, nucleolus, mitochondria and endoplasmic reticulum displayed no conspicuous changes and glycogen particles were well preserved; however, occasionally mitochondria appeared to have curled or circular cristae. The liver cell membrane facing the Disse’s space did not appear to be significantly altered and the Disse’s space had a normal width.
The bile canaliculus shows to be remarkably dilated and completely occluded with bile, granular and laminated in appearance.

No direct communication between the bile canaliculus and the Disse’s space was noted.

DISCUSSION

Thioridazine has been used for mental and emotional disturbances in Japan since 1962, and is one of the tranquilizers belonging to the phenothiazine group. Cases of toxic hepatitis induced by this drug have not been reported to date. Biochemical and histological data of this case indicated that this was a cholestatic type like other phenothiazine induced hepatitis, and allergic processes in the development of hepatic injuries in this case were suggested by such clinical findings as eosinophilia, skin rash and itching.

The electron microscopic studies of cholestatic type of drug induced hepatitis by Schaffner, Reichel, Orlandi and Steiner have indicated a characteristic change of the bile canaliculus, associated with deposition of electron dense materials, presumably bile, in the cytoplasm of the liver cell. Although there is some difference in detail, our observation of this case generally coincide with the reports.

Such canalicular changes can be produced primarily by the direct action of the
Dilated bile canaliculus contains electron dense, crystalline like bile material in the lumen. The cytoplasmic band of the liver cell facing the canaliculus reveals to be denser and devoid of vesicles and free ribosomes. Electron dense materials, presumed to be bile and mostly laminated in appearance, are observed in the cytoplasm of the liver cell.

Fig. 4. Electron micrograph. ×12,000

Drug or by an allergic reaction on the canalicular membrane and secondarily by interference of the bile flow. The dilatation of the bile canaliculus with bile retention is readily explained by increased hydrostatic pressure in extrahepatic obstructive jaundice, but in intrahepatic cholestasis, the mechanism of bile retention in the bile canaliculus is not well established. Edematous microvilli could occlude the canaliculus as Steiner and Tanikawa have suggested, or the altered canalicular membrane could possibly excrete abnormal biliary constituents which result in bile retention and formation of bile plugs which locally obstruct bile flow. It has not been clarified as whether the involvement of the bile ductule is responsible for the bile retention in intrahepatic cholestasis.

The bile stasis in the cytoplasm of the liver cell, observed electron microscopically as electron dense granules, would be important in the pathogenesis of bile regurgitation. This has been discussed by Tanikawa and Orlandi.

SUMMARY

The liver biopsy specimen taken from a patient with Thioridazine induced hepatitis...
The Kupffer cell contains large dense bodies and small dense granules in the cytoplasm. The liver cell has many lysosomes.

was studied under electron microscope. The bile canaliculus showed to be irregularly dilated with loss or altered microvilli and bile retention in the lumen. Numerous electron dense granules, presumably a bile component, were observed in the cytoplasm of the liver cell and Kupffer cell. The changes of the cytoplasmic organelles in the liver cell, however, revealed to be minimal. The pathogenesis of the hepatic injuries in this case has been, discussed.

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REFERENCE

