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Gallbladder bile contains nucleating-promoting activity that binds to concanavalin A. The activity was found in gallbladder bile from cholesterol gallstone patients but also in gallbladder bile from patients without stones and patients with pigment stones. Bile from patients with multiple cholesterol gallstones contained high concanavalin A-binding nucleation-promoting activity. The activity was much lower in bile samples from pigment stone patients, patients without stones and patients with a solitary cholesterol stone. Serum contained very little activity and no concanavalin A-binding nucleation-promoting activity could be demonstrated in gallbladder mucosa. This suggests that concanavalan A-binding nucleation promoter is produced in the liver or bile duct epithelium. The activity was fully resistant to digestion with pronase but was heat labile and could be destroyed by prolonged incubation with a mixed glycosidase preparation indicating that sugar residues are important for this activity. On a Superose 12 gel permeation column, promoting activity eluted in two major peaks at apparent molecular weights of 150 ± 30 kD (n = 5) and < 5 kD, respectively.

The mobility on the column was not influenced by pronase digestion. The factor with the higher molecular weight could be isolated further by polyacrylamide gel electrophoresis under non-denaturating conditions. On sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the apparent molecular weight of the glycoprotein was 130 kD. In conclusion, gallbladder bile contains nucleating-promoting activity that binds to concanavalin A. The activity is increased in bile from patients with multiple cholesterol gallstones and could therefore play an important role in the pathogenesis of gallstone disease.

Comment

Abnormal rapid nucleation of cholesterol from supersaturated gallbladder bile is of key importance in primary gallstone formation. However, the degree of supersaturation in bile is not related to the presence of cholesterol crystals or to the time required for their nucleation. Therefore, nucleation-promoting factors in lithogenic bile have been postulated.

Groen et al. have isolated by concanavaline A-Sepharose chromatography of gallbladder bile a glucose-/mannose-containing 130-kD glycoprotein with strong cholesterol nucleation-promoting activity of model biles. The activity was found in the majority of gallbladder biles investigated and high nucleation-promoting activity titers were observed in biles from patients with multiple cholesterol stones. The activity titer in bile was not correlated to total protein content, cholesterol saturation index and total lipid concentration. Furthermore and more important, according to a prior publication of the authors (Clin Chim Acta 1987;165:292–302), no correlation between the nucleating promoting activity titer and the cholesterol nucleation time has been observed. The data of Groen et al. are of particular interest and the relationship between the 130-kD glycoprotein and the pathogenesis of multiple cholesterol gallstones seems to be evident.

The low nucleation-promoting activity titer in biles from patients with solitary cholesterol stones, indistinguishable from the titers in biles of patients with pigment stones or no stones, is surprising and difficult to explain. It points to an exclusive role of the isolated glycoprotein in the pathogenesis of multiple cholesterol gallstones.

However, the finding of low-activity titers in biles of patients with solitary cholesterol gallstones...
and the missing correlation between activity titer and cholesterol nucleation time clearly shows that the 130-kD glycoprotein could not be the sole nucleation-promoting factor. This underscores the multifactorial etiology of cholesterol gallstone disease and should stimulate further investigation of the pathophysiology of cholesterol gallstone formation.

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BILIARY LITERATURE SURVEY

Aoki T, Tanimura H, Kawashima H, et al. Cholescin-
Albert MB, Fromm H, Borstelmann R, et al. Successful and the missing correlation between activity titer the pathophysiology of cholesterol gallstone for-
Ditzel H, Schaffalitzky-de-Muckadell OB. Endoscopic sphincterotomy in acute cholangitis due to choledo-
Hall RI, Ingoldby CJ, Denyer ME. Periampullary di-
Josephs LG, Birkett DH. Electrohydraulic lithotripsy
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Rege RV, Dawes LG, Moore EW. Biliary calcium secretion in the dog occurs primarily by passive convection and diffusion and is linked to bile flow. J Lab Clin Med 1990;115:593–602.


