Abnormal Lipid Metabolism in Clinical and Experimental Cholestasis

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The present studies mainly deal with abnormalities in LDL, lipoprotein-X (LP-X) and lipoprotein-Y (LP-Y); and HDL fractions, a large molecular weight HDL, obtained from plasma of patients with cholestasis, in relation to changes in lecithin-
cholesterol acyltransferase (LCAT) and hepatic triglyceride lipase (H-TGL) activities. Relationship between retinol-binding protein (RBP) and taste acuity in cholestasis is also described in this paper.

I. Abnormalities in LDL fraction
(LP-X and LP-Y)

When plasma LDL (d=1.019-1.063) in cholestasis was subjected to hydroxyapatite column chromatography, LP-X, LP-Y and LDL were found to be successively eluted, as described by Kostner et al.15.

1) LP-X: The isolated LP-X revealed electron microscopically a rouleaux formation of a discoidal plate (80×500Å), showing a distinct lipid composition (PL, 66%; FC, 24%). Quantitative method of plasma LP-X estimation was developed by the measurement of PL content in the portion which migrates to the cathode on Bactoagar electrophoresis. A positive correlation between plasma LP-X level and diameter of anterior segment bile duct on PTC was obtained in 51 patients with extrahepatic cholestasis (r=0.621, P<0.001), and plasma LP-X level was rapidly decreased and then disappeared usually within 2 weeks after PTG-drainage. The majority of our patients (about 78%) with extrahepatic cholestasis, particularly due to malignancy, showed abnormal LP-X concentrations higher than 150 mg/dl, that was found in approximately 7% of patients with intrahepatic cholestasis (i.e., primary biliary cirrhosis).

Two subfractions of LP-X; LP-X1 and LP-X2 were demonstrated in plasma of patients with cholestasis by zonal ultracentrifugation according to the method of Patsch et al.2. Only LP-X1, however, was observed in bile lipoprotein with or without native serum and the LP-X positive plasma obtained from 2 patients after Intralipid infusions. On the other hand, LP-X2 was found to be higher than LP-X1 in patients with extrahepatic cholestasis and dominant in those with intrahepatic cholestasis. These results strongly suggest the distinct different mechanism for appearance of LP-X1 and LP-X2 in plasma.

2) LP-Y: The isolated LP-Y showed electron microscopically a spherical particle with a diameter of about 400 Å, exhibiting triglyceride-rich in contents (21.3%). At present, LP-Y is considered to play an important role in development of hypertriglyceridemia of patients with cholestasis, although its underlying mechanism remains clarified. We have claimed that decrease in H-TGL activity is responsible for, at least partly, the appearance of LP-Y from the following findings: a) Plasma H-TGL activity was found to be extremely reduced, whereas lipoprotein lipase (LPL) activity remained unchanged in the patients with cholestasis, b) A negative correlation between plasma LP-Y level and H-TGL activity of the liver was obtained after ligation of the bile duct in rats (r=-0.849, P<0.01), and c) In vivo and in vitro addition of partially purified H-TGL, but not LPL, brought about a selective reduction or disappearance of LP-Y found in the ligated rats.

II. Abnormalities in HDL fraction

Changes in plasma HDL fraction have been demonstrated not only quantitatively, but also qualitatively in patients with cholestasis3. When HDL fraction (d=1.063-1.21) was subjected to gel filtration on Sephadex G-200 column, a large molecular weight HDL eluting faster than that of normal HDL was observed. The large HDL particle exhibited a distinct lipid composition (high FC and very low CE), and a dominant proportion of apo-E on SDS-polyacrylamide electrophoresis as well as a rouleaux formation of a discoidal plate (40×200Å) by electronmicroscopical examinations. These properties are assumed to be quite similar to “nascent” HDL.

III. Abnormalities in plasma transport of vitamin A (RBP)

Recent studies4 have demonstrated that vitamin A (retinol) is transported in plasma by a specific binding protein; RBP (mol
Supplementary: A study for hypercholesterolaemia

wt, 20,000) which is associated with prealbumin; PA (mol wt, 55,000) as a protein-protein complex. Plasma RBP level is kept constant by synthesis and secretion from the liver, and by degradation in the kidney (one of rapid turnover proteins with a biological half-life of 13 hr). Vitamin A is assumed to be taken up through a specific receptor for RBP which is located on the surface of target cells (i.e., the retina, reproductive organ, taste buds etc.).

Abnormally high threshold of taste acuity, measured with a use of electrogastrometer (Lyon Co., Tokyo), was decreased and restored toward normal immediately after PTC-drainage in patients with cholestasis, with a concomitant restoration of daily food intakes. An inverse correlation between threshold of taste acuity and plasma RBP was observed \( r = -0.86, P < 0.001 \), strongly suggesting that plasma RBP plays an important role in maintenance of taste acuity.

Plasma RBP level was rapidly decreased to about 30% one day after ligation of the bile duct in rats, whereas restored toward normal within 8 hr after release of the ligation.

These results strongly suggest that RBP is one of the useful indicators for hepatocellular damage in cholestasis.

SUMMARY

The abnormalities in lipid metabolism such as LP-X, LP-Y and large HDL observed in cholestasis bring about morphological changes in the biomembrane; in particular, the red blood cells through enhanced osmotic resistance and decreased fluidity. Moreover, plasma RBP may correlate with maintenance of taste acuity through supply of vitamin A to the target tissue.

REFERENCES