(6) Pathogenesis of Hyperlipidemia in Biliary Obstruction

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Biliary obstruction is associated with elevated plasma cholesterol and phospholipid. Regurgitation of bile and the increased synthesis of cholesterol have been considered as major causes for the secondary hyperlipidemia due to the obstruction of bile duct. We studied the pathogenesis of the plasma lipid increment in the biliary obstruction with particular reference to the transport and metabolism of cholesterol, lecithin and bile acid.

(I) Transport and metabolism of plasma cholesterol and lecithin

a) Cholesterol metabolism

After addition of 14C-cholesterol linoleate as complexed with rat plasma into the blood perfusate of isolated rat liver, liver removed it actively as well as 14C-cholesterol and 14C-palmitate. Since it has been demonstrated that cholesterol ester was hydrolyzed by the liver and that the liver also released cholesterol to plasma in the form incorporated to VLDL, there is a circuit of cholesterol between the intravascular pool and the liver through the esterified form. In order to study the importance of plasma LCAT for maintaining plasma level of cholesterol ester, the role of liver and plasma was studied. Cholesterol esterification occurred at a negligible rate unless LCAT was present in the perfusate of the isolated rat liver. Esterification proceeded with time in the blood perfusate at relatively constant rate. Thus plasma LCAT plays major role in the esterification of cholesterol in the plasma.

b) Origin and disappearance of LCAT

When active rat plasma was used in the liver perfusion system, the values for LCAT activity decreased more rapidly than did those of mock system without liver. This result indicates that liver functions in the inactivation of LCAT. We verified the secretion of esterifying activity by the liver by perfusing the isolated rat liver with an artificial medium. Each time plasma-free medium was changed to eliminate the possibility of release of LCAT that had been trapped in the liver, and the same results were reproduced.

c) Regulation of LCAT activity

LCAT was determined by the method of Portman & Sugano and the values were compared with those obtained using the thin layer chromatography which estimates the production of lysolecithin. Both methods agreed in general. When squirrel monkeys were fed high butter and cholesterol (0.1 g/100 Kcal), they developed hyper-
cholesterolemia and vascular sclerosis. As the plasma level of cholesterol increased in two weeks after the start of the diet, LCAT activity started being higher. There was a significantly high positive correlation \((r=0.88)\) between the plasma level of cholesterol and LCAT activity.

d) Transport and metabolism of lecithin

\(^{14}\text{C}-\text{lysolecithin}\) was injected to squirrel monkeys intravenously. The die-away curves of \(^{14}\text{C}-\text{lysolecithin}\) from plasma and the timing of appearances of other \(^{14}\text{C}\)-labeled moieties in plasma and other tissues demonstrated a complex pattern of metabolic reactions. The specific activity of lecithin peaked first in liver, then in plasma. The sequence of specific activity peaks shows that liver lysolecithin is a precursor of liver lecithin which in turn is a precursor of plasma and bile lecithin. Therefore, lecithin has a circuit between the intravascular pool and the liver through lysolecithin like cholesterol, both of which are the substrates catalyzed by LCAT.

(II) Secondary hyperlipidemia in obstructive jaundice

a) Feedback control of cholesterol synthesis in the liver

Cholesterol and bile acid synthesis in the liver is regulated by the enterolymphatic and enteroportal circulation of cholesterol and bile acid. Diversion of bile by external fistula and the ligation of the bile duct are the conventional ways of interrupting the enterohepatic circulation (EHC). When bile was diverted in the squirrel monkey, biliary lipid composition changed rapidly. Total and individual bile acids and lecithin concentration in the hepatic bile dropped rapidly after the beginning of bile diversion. In contrast, cholesterol concentration changed to lesser extent or even increased in some cases.

In several monkeys, \(^{14}\text{C}-\text{cholic}\) and \(^{14}\text{C}-\text{chenodeoxycholic acid}\) were given intravenously prior to diversion. The specific activity of the individual bile acid in the hepatic bile decreased after the ligation of biliary duct, showing that the new synthesis of bile acid started in response to the interruption of EHC.

In the case of biliary diversion, the molar percent of cholesterol in the bile among biliary lipid (cholesterol, lecithin, bile acid) increased with time in contrast with that of bile acid. This implies that the overall production of new synthesis of cholesterol exceeded that of bile acid stimulated by EHC interruption, even though it is said that HMG-CoA reductase and 7α-hydroxylase change almost concomitantly (Danielsson\(^5\)). Another method of EHC interruption is the bile duct ligation. Bile ducts of dogs were ligated and T-tubes were inserted into the ducts to monitor and compare the changes of major biliary lipid in the hepatic bile in the plasma for three weeks. Plasma and biliary lipid changed in the opposite direction. In the plasma, cholesterol, lecithin and bile acid increased 24 hours after ligation, whereas bile acid, lecithin and cholesterol declined in the bile, supporting the report of Danielsson\(^6\) that cholesterol and bile acid synthesis was suppressed by 24 hours after ligation.

Effects of those two ways of EHC interruption on the cholesterol synthesis in the liver are different in terms of pressure inside the bile duct or the regurgitation of bile
component into hepatic cells, but the common phenomenon in both situations is that the feedback control of cholesterol and bile acid synthesis in the liver operates from the relatively early stage after EHC interruption, although the individual effect of cholesterol or bile acid could not be differentiated.

b) Changes of bile acid and lecithin

Fatty acid composition of lecithin of plasma, liver and bile was compared in the dog before and after the ligation. Although the regurgitation of bile lecithin into plasma in the obstruction could not be demonstrated, palmitate was dominant in plasma, bile and liver in the bile duct ligation, which was dominant in bile prior to the ligation. Bile acid and lecithin changed almost concomitantly in plasma and bile in almost all cases and conditions such as bile diversion or bile duct ligation, implying the close relationship between them.

c) LCAT activity in the obstructive jaundice (Fig. 1)

In the hepatobiliary disease in man LCAT was reduced, but in some cases of obstructive jaundice LCAT was found to be high. Since LCAT enzyme is produced and secreted from hepatic cell, LCAT was determined in acute obstruction in rat in order to eliminate complex factors which are caused by hepatic cell damage. Plasma cholesterol, lecithin, and bile acid increased as did cholesterol ester 24 and 48 hours after bile duct ligation, whereas triglyceride and free fatty acid remained unchanged. LCAT activity was significantly elevated at 24 and 48 hours compared with the value before the ligation, being compatible with the previous result that plasma cholesterol level is one of the factors regulating LCAT, although the form of cholesterol as lipoprotein may be important as substrate. Increased bile acid did not reach the range in which LCAT was inhibited in vitro.

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![Chart showing changes in TC, EC, and LCAT before and after 24 and 48 hours](image)

**Fig. 1.** LCAT activity in acute biliary obstruction in rat.

TC: total cholesterol, EC: esterified cholesterol, mean±SEM, n=5.
Summary

Increment of cholesterol and lecithin in plasma in obstructive jaundice is the result of regurgitation of bile and the reflection of complex metabolic changes in liver. EHC interruption is one of the major factors which have an effect on the synthesis of cholesterol and bile acid in liver.

In acute biliary obstruction, plasma LCAT activity is elevated with an increment of free and esterified cholesterol in plasma. But in the chronic stage with liver cell damages LCAT is reduced and the ratio of esterified to total cholesterol declines (Fig. 2).

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Fig. 2. Pathogenesis of secondary hyperlipidemia due to biliary obstruction.

Reference